Compound No.	X	Y	m	R
3-158	MeO N	0	2	Н
3-159	MeO N	0	1	MeO
3-160	MeO N	s	1	Н
3-161	Pr N MeO	0	1	Н
3-162	Pr N MeO	s	1	Н
3-163	MeO N	0	1	н
3-164	MeO N	0	1	Н

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Table 3 (cont.)

Compound No. х R Y m 3-165 S 1 Н MeO Me 3-166 0 1 Н EЮ 0 3-167 ı MeO ΕťΟ 3-168 0 ١ Cl Me 3-169 0 2 н **EtO** 3-170 0 3 Н EtO

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Table 3 (cont.)

Compound No. Х Y R m Me 3-171 s Н 1 EtO Me 3-172 s Et 4 Me 3-173 0 1 н Me 3-174 s н 1 3-175 0 1 н 3-176 0 3 н

Compound No.	X	Y	m	R
3-177	Me N BuO	0	1	н
3-178	Me N /BuO	0	1	н
3-179	sBuO N	0	1	Н
3-180	/BuO N	0	1	н
3-181	Pr N N	0	1	н
3-182	Me N N	0	1	н
3-183	MeO NeO N	0	1	н

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Table 3 (cont.)

Compound No. x Y m R Me 3-184 0 1 Н MeO. Me 0 1 3-185 н EtO. Me I N 3-186 0 1 Н Me 3-187 0 1 Н Me 3-188 0 1 Н 0 3-189 1 Н

5	Compound No.	Х	Y	m	R
10	3-190	EI N	0	1	н
15	3-191	Mc N	0	1	н
26	3-192	CF3 Ne	0	1	н
35	3-193	CF3 N	0	1	Н
40	3-194	Me N	0	1	Н
45		CF ₃			
50	3-195	CF3 N N	0	1	н
55		Cr3			

5					_
	Compound No.	Х	Y	m	R
10	3-196	Br N N N	0	1	Н
15					
20	3-197	F N N N	0	1	н
25	3-198	Br N N N Me	0	2	н
30		Me Me			
35	3-199	Me N N	0	1	н
40	3-200	HO N	0	1	н
50	3-201	Me N	0	1	н
55	ł	Ме			

Compound No.	X	Y	m	R
3-202	2 2 2 - g	0	1	н
3-203	F N N	0	1	н
3-204	Br N N	0	1	Н
3-205	Me N N	0	1	Н
3-206	Me Me N N N N N N N N N N N N N N N N N	0	1	н
3-207	Me Mc N	0	2	н

Compound No.	X	Y	m	R
3-208	Me Me N N	0	3	Н
3-209	Me Me N N N N N N N N N N N N N N N N N	S	1	Н
3-210	Me Me N N	0	l	Me
3-211	Me Me N N N N N N N N N N N N N N N N N	0	1	MeO
3-212	Me Me N N N Me	0	1	Ci
3-213	Me N	0	1	н

Table 3 (cont.)

Compound No.	X	Y	m	R
3-214	Me N	0	2	н
3-215	Me N	0	3	н
3-216	Me N N	0	4	н
3-217	Me N	0	5	н
3-218	Me N	0	1	MeO
3-219	Me N	0	1	CI
3-220	Me N	S	1	Н
3-221	Me N	S	3	н

Compound No.	Х	Y	m	R
3-222	EI-N N	0	1	н
3-223	Et N	S	1	н
3-224	Pr N	0	1	н
3-225	Pr N	0	1	CI
3-226	ĴPr N	0	1	н
3-227	IPT N	S	1	н
3-228	Bu N	0	1	н
3-229	Bz N	0	1	н

Table 3 (cont.)

Compound No.	X	Y	m	R
3-230	Bz N	0	3	Н
3-231	Bz N	s	I	н
3-232	Me N	0	1	н
3-233	Et N	0	1	н
3-234	Bz N	0	1	н
3-235	Bz N	s	1	Н
3-236	Me N Me	0	1	Н

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Table 4

Compound No.	Х	Υ.	m	R
4-1	$\bigcirc \bigvee_{N-H}^{N-H}$	0	1	Н
4-2	○ N N N	0	2	н
4-3	○ N H	0	3	н
4-4	N N H	0	4	н
4-5	N N H	0	5	MeO
4-6	N H	S	1	н
4-7	N H	0	1	MeO
4-8	N N H	0	1	Cl

Compound No.	X	Y	m	R
4-9	ON H	0	1	Ме
4-10	○\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	s	1	MeO
4-11	N N Me	0	1	н
4-12	N Me	0	2	н
4-13	N N Me	0	3	н
4-14	N N Me	0	4	н
4-15	N N Me	0	5	Н
4-16	N N Me	S	1	Н

Compound No.	Х	Y	m	R
4-17	N N Me	S	2	н
4-18	N N Me	0	1	MeO
4-19	N N Me	0	1	EtO
4-20	N N Me	0	1	CI
4-21	N N Me	0	1	F
4-22	N N Me	0	1	Me
4-23	N Ne	0	1	íРт
4-24	N Ne	0	2	Et

Compound No.	X	Y	m	R
4-25	N N Me	s	1	Cl
4-26	○ N N Me	S	1	Me
4-27	N Et	0	1	н
4-28	N N-Et	0	2	н
4-29	○ N N Ex	0	3	#Bu
4-30	$\bigcirc \bigvee_{N \atop Et}^{N}$	0	1	Me
4-31	N N Et	0	1	MeO
4-32	N Et	S	1	н

Compound No.	X	Y	m	R
4-33		s	1	PrO
4-34		S	1	Me
4-35	$\bigcirc \bigvee_{N=1 \atop Pr}^{N}$	0	1	н
4-36	$\bigcup_{\substack{N\\Pr}}^{N}$	0	3	н
4-37	$\bigcirc \stackrel{N}{\underset{P_{r}}{\triangleright}}$	0	1	F
4-38	$\bigcirc \stackrel{N}{\underset{Pr}{\longleftarrow}}$	s	1	Н
4-39	N IPr	0	1	Н
4-40	○ N N Pr	0	2	Н

Compound No.	X	Y	m	R
4-41	N N IPr	S	1	н
4-42	N N iPr	s	5	CI
4-43	OTN Bu	o	1	н
4-44	$\bigcirc \bigvee_{N}^{N}$	0	4	н
4-45	N N Bu	S	1	н
4-46	MeO N N	0	1	н
4-47	Meo N H	0	3	н
4-48	MeO N N N N N N N N N N N N N N N N N N N	S	1	н

5	Compound No.	Х	Y	m	R
10	4-49	MeO N Me	0	1	Н
15	4-50	MeO N Me	0	2	н
20	4-51	MeO Ne	0	3	н
30	4-52	MeO N Me	0	4	н
36	4-53	MeO N N N N N N N N N N N N N N N N N N N	0	5	Н
40	4-54	MeO N N N N N N N N N N N N N N N N N N N	S	1	н
45	4-55	MeO N N Me	S	2	н
50	4-56	MeO N N N N N N N N N N N N N N N N N N N	0	1	Ме
		1.16			

Compound No.	X	Y	m	R
4-57	MeO N N Mc	0	1	MeO
4-58	MeO N Me	0	1	F
4-59	MeO N N N N N N N N N N N N N N N N N N N	0	1	CI
4-60	MeO N Et	0	1	н
4-61	MeO N Et	0	2	н
4-62	MeO N Et	0	1	MeO
4-63	MeO N Et	S	1	Н
4-64	MeO N Pr	0	l,	Н

Compound No.	_ · _ x	Y	m	R
4-65	MeO N Pr	S	1	н
4-66	MeO N N IPr	0	1	н
4-67	MeO N N N N N N N N N N N N N N N N N N N	0	1	н
4-68	MeO N N N N N N N N N N N N N N N N N N N	S	1	Н
4-69	EtO N Me	0	1	Н
4-70	EtO N Me	0	1	MeO
4-71	EtO N Me	0	1	CI
4-72	Exo N N Me	o	2	Н

Compound No.	Х	Y	m	R
4-73	EtO N N Me	0	3	н
4-74	EtO N N Me	s	1	н
4-75	EtO N N Me	S	4	Et
4-76	PrO N Me	0	1	н
4-77	Pro N Me	s	1	н
4-78	/Pro N Me	0	1	н
4-79	/Pro N Me	0	3	н
4-80	BuO N N N N N N N N N N N N N N N N N N N	0	1	н

Compound No.	X	. Y	m	R
4-81	ßuO N N N N N Me	0	1	н
4-82	sBuO N N N N N N N N N N N N N N N N N N N	0	1	Н
4-83	/BuO N N Me	0	1	н
4-84	BuO N Pr	0	. 1	Н
4-85	B ₂ O N N N N N N N N N N N N N N N N N N N	0	1	н
4-86	MeO N N N Me	0	1	н
4-87	MeO N N N N N N N N N N N N N N N N N N N	0	1	н

5	Compound No.	X	Y	m	R
10	4-88	FIO N Me	0	1	Н
15	4-89	F N N Me	0	1	Н
25	4-90	F N N Me	0	1	Н
30	4-91	CI N N Me	0	1	н
40	4-92	CI N Et	0	1	н
45	4-93	Et N N Me	0	1	н
50	4-94	Br N N N N N N N N N N N N N N N N N N N	0	1	н

Compound No.	X	Y	m	R
4-95	CF ₃ N N N N N N N N N N N N N N N N N N N	0	1	Н
4-96	CF ₃ N N N N N N N N N N N N N N N N N N N	0	1	Н
4-97	○ N N CF ₃ Me	0	1	Н
4-98	CF ₃ N N Me	0	1	н
4-99	Br N N N N N N N N N N N N N N N N N N N	0	1	Н
4-100	F N N N N N N N N N N N N N N N N N N N	0	1	н
4-101	Br. N N N N N N N N N N N N N N N N N N N	0	1	н

Compound No.	X	Y	m	R
4-102	tBu N N N N N N N N N N N N N N N N N N N	0	1	Н
4-103	HO N N N N N N N N N N N N N N N N N N N	0	1	н
4-104	N N Me Me	0	1	н
4-105	CI N N Me	0	1	н
4-106	F N N Me	0	1	н
4-107	Br N N Me	0	1	н
4-108	N N Cl Me	0	1	н

Compound No.	X	Y	m	R
4-109	HO N N N N N N N N N N N N N N N N N N N	0	1	Н
4-110	HO N N N N N N N N N N N N N N N N N N N	0	2	н
4-111	HO N N N N N N N N N N N N N N N N N N N	0	3	Н
4-112	HO Ne Ne	S	1	н
4-113	Me N N N N N N N N N N N N N N N N N N N	0	1	Me
4-114	Me N N N N N N N N N N N N N N N N N N N	0	1	MeO
4-115	Me N N N N N N N N N N N N N N N N N N N	0	1	CI

Table 4 (cont.)

Compound No.	X	Y	m	R
4-116	N N N H	0	1	Ħ
4-117	N H	S	1	н
4-118	N N Me	0	1	н
4-119	N N Me	0	2	н
4-120	N N Me	0	3	н
4-121	N N Me	0	4	н
4-122	N N Me	0	5	Н

Compound No.	X	Y	m	R
4-123	N N N Me	0	1	MeO
4-124	N N Me	0	1	CI
4-125	N N Me	S	1	н
4-126	N N Me	s	3	н
4-127	N N E	0	1	н
4-128	N N Et	S	1	н
4-129	N N Pr	0	1	н

Table 4 (cont.)

Compound No.	X	Y	m	R
4-130	N N Pr	0	1	CI
4-131	N N IPt	0	1	н
4-132	N N iPr	S	1	н
4-133	N N Bu	0	1	н
4-134	N N Bz	0	1	н
4-135	N N Bz	0	3	н
4-136	N N Bz	S	1	н

Compound No.	X	Y	m	R
4-137	N N Me	0	1	н
4-138	N N E	0	1	н
4-139	N N Bz	0	1	н
4-140	N N Bz	S	1	н
4-141		0	1	н
4-142	N N Me	0	1	н
4-143	N N Me	0	1	Н

Compound No.	X	Y	m	R
4-144	N Me	0	1	н
4-145	N N Mc	s	1	н
4-146	Me N	o	1	Н
4-147	Me N	0	2	н
4-148	Me N	0	3	н
4-149	Me N	0	4	н
4-150	Me N	0	5	Н

Compound No.	Х	Y	m	R
4-151	Me N	S	1	н
4-152	Me N	S	2	н
4-153	Me N	0	1	Ме
4-154	Me N	o	2	Me
4-155	Me N	0	1	F
4-156	Me N	0	1	Cl
4-157	Et N	0	1	н

Compound No.	X	Y	m	R
4-158	MeO N	0	2	Н
4-159	MeO N	0	1	MeO
4-160	MeO N	s	1	н
4-161	MeO N	0	1	н
4-162	Pr N MeO N	s	1	н
4-163	MeO N	0	1	Н
4-164	MeO N	0	1	н

Compound No.	X	Y	m	R
4-165	MeO N	S	1	н
4-166	EtO Ne	0	1	н
4-167	EtO N	0	1	MeO
4-168	Me N N	0	1	CI
4-169	EtO N	0	2	н
4-170	EtO N	0	3	н

Table 4 (cont.)

Compound No.	X	Y	m	R
4-171	EtO Ne	S	1	н
4-172	EtO N	S	4	Et
4-173	Pro N	0	1	н
4-174	Pro N	S	1	Н
4-175	Me N N	0	1	н
4-176	Me N N	0	3	Н

5	Compound No.	X	Y	m	R
10	4-177	BuO N	0	1	н
15	4-178	Me N	О	1	Н
25	4-179	sBuO Ne	O	1	Н
30	4-180	/BuO N	0	1	н
35	4-181	Pr N N	0	1	Н
45	4-182	Me N BzO N	0	1	Н
50	4-183	MeO N	0	1	Н
55		Me			

Compound No.	Х	Y	m	R
4-184	MeO NeO N	0	1	н
4-185	EiO N N	0	1	н
4-186	Me N N	0	1	н
4-187	Me N	0	1	н
4-188	CI N N	0	1	н
4-189	CI PI	0	1	н

	Compound No.	X	Y	m	R
	4-190	Et N	0	1	Н
	4-191	Me N N	0	1	н
	4-192	CF ₃ Me	0	1	Н
	4-193	CF3 Ne	0	1	Н
	4-194	Me N CF3	0	1	Н
	4-195	CF3 N Me	0	1	н

Compound No.	Х	Y	m	R
4-196	Br Ne Ne Ne Ne	0	1	Н
4-197	F N N	0	1	н
4-198	Br N N N N N N N N N N N N N N N N N N N	0	2	н
4-199	Me N N	0	1	н
4-200	HO N	0	1	н
4-201	Me N Me	0	1	н

Compound No.	X	Y	m	R
4-202	Me N CI	0	1	Н
4-203	F N N	0	1	Н
4-204	Br N N	0	1	н
4-205	Me N CI	0	1	н
4-206	Me Me N N N N N N N N N N N N N N N N N	0	1	Н
4-207	Me Me N N N	0	2	н

Compound No.	X	Y	m	R
4-208	Me Ne No Me	0	3	Н
4-209	Me Me N N N	S	1	Н
4-210	Me N N N N N N N N N N N N N N N N N N N	0	1	Ме
4-211	Me Me N N N Me	0	1	MeO
4-212	Me Me N N Me	0	1	CI
4-213	Me N	0	1	н

Compound No.	X	. Y	m	R
4-214	Me N	0	2	Н
4-215	Me N	0	3	н
4-216	Me I N	0	4	н
4-217	Me N N	0	5	н
4-218	Me N	0	1	MeO
4-219	Me N	0	1	CI
4-220	Me N	S	1	н
4-221	Me N	s	3	н

Compound No.	Х	Y	m	R
4-222	Et N	О	1	Н
4-223	Et N	s	1	Н
4-224	Pr N	0	1	н
4-225	Pr	0	1	Cı
4-226	₽r N	0	1	н
4-227	IPr N	s	1	Н
4-228	Bu N	0	1	н
4-229	Bz N	0	1	н

Compound No.	X	Y	m	R
4-230	Z Z Z - RE	0	3	н
4-231	Bz N	S	1	н
4-232	Me N	0	1	н
4-233	Et N	0	1	н
4-234	Bz N	0	1	н
4-235	Bz N	S	1	н
4-236	Mc N N Me	0	1	Н

Table 5

Compound No.	X	Y	m	R
5-1	N H	0	1	н
5-2	○ N H	0	2	н
5-3	N H H	0	3	н
5-4	N N H	0	4	н
5-5	N H H	0	5	MeO
5-6	○ N H	s	1	н
5-7	○ N H	0	1	MeO
5-8	○ N N N	0	1	CI

Compound No.	X	Y	m	R
5-9	N-H	0	1	Me
5-10	$\bigcirc \bigvee_{N}^{N}$	S	1	MeO
5-11	N Ne	0	1	н
5-12	N N Me	0	2	Н
5-13	N N Me	0	3	Н
5-14	N Me	0	4	Н
5-15	N N Me	0	5	н
5-16	N N Me	s	1	Н

Table 5 (cont.)

5	Compound No.	Х	Y	m	R
10	5-17	N-Me	S	2	н
15	5-18	N_N_Me	0	1	MeO
20	5-19	z-Ne	0	1	EtO
30	5-20	$\bigvee_{z - Me}$	0	1	СІ
35	5-21	\bigvee_{N-Me}^{N}	0	1	F
40	5-22	N N Me	0	1	Me
45	5-23	N-Me	0	1	<i>î</i> Pr
50	5-24	N N Me	0	2	Et
		IAIG			

Compound No.	х	Y	m	R
5-25	N N Me	s	1	СІ
5-26	N Me	S	1	Me
5-27	N Et	0	1	Н
5-28	N N Et	0	2	н
5-29	N Et	0	3	/Bu
5-30	N N Et	0	1	Ме
5-31	N Est	0	1	MeO
5-32	N Est	S	1	н

Compound No.	Х	Y	m	R
5-33	N N Et	S	1	PrO
5-34	N N Et	s	1	Me
5-35	N Pr	0	1	н
5-36	N Pr	0	3	н
5-37	OTN →	0	1	F
5-38	N Pr	S	1	Н
5-39	N _{IPr}	0	1	Н
5-40	N N IPr	0	2	Н

Compound No.	- х	Y	m	R
5-41	N N iPr	S	1	н
5-42	N N Pr	s	5	CI
5-43	O N Bu	0	1	н
5-44	N _N Bu	0	4	н
5-45	©\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	s	1	н
5-46	MeO N H	0	1	н
5-47	MeO N H	0	3	н
5-48	MeO N H	S	1	н

Compound No.	X	Y	m	R
5-49	MeO N N N N N N N N N N N N N N N N N N N	0	1	н
5-50	MeO Ne	0	2	н
5-51	MeO N Mc	0	3	н
5-52	MeO Ne	0	4	Н
5-53	MeO N Me	0	5	Н
5-54	MeO N Me	S	1	Н
5-55	MeO N Me	S	2	Н
5-56	MeO N Me	0	1	Me

Compound No.	X	Y	m	R
5-57	MeO N N N N N N N N N N N N N N N N N N N	0	1	MeO
5-58	MeO Ne	0	1	F
5-59	MeO N Me	0	1	СІ
5-60	MeO N Et	0	1	н
5-61	MeO . Et	0	2	н
5-62	MeO N N N N N N N N N N N N N N N N N N N	0	1	MeO
5-63	MeO N N Et	s	1	н
5-64	MeO N N Pr	0	1	Н

Compound No.	X	Y	m	R
5-65	MeO N Pr	S	1	н
5-66	MeO N N IPr	0	1	Н
5-67	MeO N N N N N N N N N N N N N N N N N N N	0	1	н
5-68	MeO N N N N N N N N N N N N N N N N N N N	s	1	н
5-69	EtO N Me	0	1	н
5-70	EtO N Me	0	1	MeO
5-71	EtO N N Me	0	1	а
5-72	EIO N Me	0	2	н

Compound No.	X	Y	m	R
5-73	EtO N N Me	0	3	н
5-74	ExO N N Me	S	1	н
5-75	EtO N Me	s	4	Et
5-76	Pro N Me	0	1	н
5-77	Pro N Me	s	1	н
5-78	iPro N Me	0	1	н
5-79	iPro N Me	0	3	н
5-80	Bu0 N Me	0	1	н

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Table 5 (cont.)

Compound No.	X	Y	m	R
5-81	iBuO N N Me	0	1	н
5-82	sBuO N N Me	0	1	н
5-83	rBuO N Me	0	1	Н
5-84	BuO N Pr	0	1	н
5-85	BzO N Me	0	1	н
5-86	MeO N N Me	0	1	Н
5-87	MeO N N N N N N N N N N N N N N N N N N N	0	1	н

Compound No.	X	Y	m	R
5-88	EtO N N Me	0	1	Н
5-89	F N N Me	0	1	Н
5-90	F N N Me	0	1	Н
5-91	CI N N N N N N N N N N N N N N N N N N N	o	1	н
5-92	CI N Et	0	1	н
5-93	Et N N Me	0	1	н
5-94	Br N N Me	0	1	н

Compound No.	Х	Y	m	R
5-95	CF ₃ N N N N N N N N N N N N N N N N N N N	0	1	Н
5-96	CF ₃ N N N N N N N N N N N N N N N N N N N	0	1	Н
5-97	CF ₃ Me	0	1	н
5-98	CF ₃ N N N N N Me	0	1	н
5-99	Br N N N N N N N N N N N N N N N N N N N	0	1	н
5-100	F N N N N N N N N N N N N N N N N N N N	0	1	Н
5-101	Br N N N N N N N N N N N N N N N N N N N	О	1	н

Compound No.	Х	Y	m	R
5-102	/Bu N N N N N N N N N N N N N N N N N N N	0	1	Н
5-103	HO N N N N N N N N N N N N N N N N N N N	0	1	н
5-104	N N Me Me	0	1	Н
5-105	CI N Me	0	1	н
5-106	$F \xrightarrow{F} N \xrightarrow{N} Me$	0	1	н
5-107	Br N N Me	0	1	Н
5-108	N N CI Me	0	1	н

Compound No.	Х	Y	m	R
5-109	HO Ne Ne	0	1	н
5-110	HO Ne Ne	0	2	н
5-111	HO Ne Me	0	3	н
5-112	HO N N N N N N N N N N N N N N N N N N N	S	1	н
5-113	Me N N N N N Me Me	0	1	Me
5-114	Me N N N N Me Me	0	ı	MeO
5-115	Me N N N N Me Me	o	1	CI

Compound No.	X	Y	m	R
5-116	N N N H	0	1	Н
5-117	H-ZZZ-H	S	1	н
5-118	N N Me	0	1	н
5-119	N N N Me	0	2	н
5-120	N N N Me	0	3	н
5-121	N N Me	0	4	н
5-122	N N Me	0	5	Н

Compound No.	X	Y	m	R
5-123	N N Me	0	1	MeO
5-124	N N Me	0	1	CI
5-125	N N Me	s	1	Н
5-126	N N Me	S	3	н
5-127	N N I B	0	1	Н
5-128	N N Es	S	1	Н
5-129	N Pr	0	1	Н
		1	l	t .

Compound No.	X	Y	m	R
5-130	N N Pr	0	1	CI
5-131	N N N IPr	0	1	н
5-132	N N IPt	s	1	н
5-133	N N Bu	0	1	н
5-134	N N Bz	0	1	н
5-135	N N Bz	0	3	н
5-136	N N Bz	S	1	н

Compound No.	Х	Y	m	R
5-137	N N Me	0	1	н
5-138	₩-Z	0	1	н
5-139	N N Bz	0	1	н
5-140	N N N Bz	S	1	н
5-141		0	1	Н
5-142	N N Me	0	1	Н
5-143	N N Me	0	1	Н

Compound No.	X	Y	m	R
5-144	N Me	o	1	н
5-145	N Me	S	I	н
5-146	Me N	0	1	Н
5-147	Me N	О	2	н
5-148	Me N	О	3	н
5-149	Me N	o	4	н
5-150	Me N	0	5	Н

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Compound No.	X	Y	m	R
5-151	Me N	S	1	Н
5-152	Me N	s	2	Н
5-153	Me N	0	1	Ме
5-154	Me N	0	2	Ме
5-155	Me N	0	1	F
5-156	Me N	o	1	CI
5-157	Fit N N N	О	1	н

Compound No.	X	Y	m	R
5-158	MeO N	o	2	Н
5-159	MeO N	0	1	MeO
5-160	MeO N	s	1	н
5-161	Pr N MeO N	0	1	н
5-162	Pr N MeO N	S	1	Н
5-163	MeO N	0	1	н
5-164	MeO N	О	1	Н

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Table 5 (cont.)

Compound No. Y R m įΒu 5-165 s 1 Н Мe 5-166 0 1 Н Me 5-167 0 1 MeO 0 5-168 1 C1 EtO Me 5-169 0 2 н EtO' 5-170 0 3 Н

Compound No.	X	Y	m	R
5-171	EtO N	S	1	н
5-172	EtO Ne	S	4	Et
5-173	Pro N	0	1	н
5-174	Me N Pro	s	1	н
5-175	Me N iPrO	0	1	н
5-176	Me N iPrO	О	3	н

	Compound No.	Х	Y	m	R
	5-177	Me N BuO	0	1	н
i	5-178	Mc N BuO	0	1	н
	5-179	Me N sBuO	0	1	Н
	5-180	/BuO N	0	1	н
	5-181	Pr N N	0	1	н
	5-182	Me N N	0	1	н
	5-183	MeO NeO N	0	1	Н

Compound No.	Х	Y	m	R
5-184	MeO Neo N	О	1	н
5-185	EIO N N	0	1	н
5-186	F N N	0	1	Н
5-187	Me N	0	1	н
5-188	CI N N	0	1	н
5-189	CI PET N	0	1	н

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Compound No.	X	Y	m	R
5-190	Et. N	0	1	Н
5-191	Mc 1	0	1	н
5-192	CF3 Ne N	0	1	н
5-193	CF3. Ne	0	1	Н
5-194	Me N CF3	0	1	Н
5-195	CF3 Ne	0	1	Н

Compound No.	X	Y	m	R
5-196	Br Ne Ne Ne	0	1	н
5-197	F N N N	0	1	н
5-198	Br N N N N N N N N N N N N N N N N N N N	0	2	н
5-199	Me N N	0	1	н
5-200	HO N N	0	1	н
5-201	Me N N Me	0	1	н

Compound No.	Х	Y	m	R
5-202	CI N	0	1	н
5-203	F N N	0	1	Н
5-204	Br N N	0	1	н
5-205	Me N N	0	1	Н
5-206	Me Me N N N N N N N N N N N N N N N N N	0	1	Н
5-207	Me N N N N N N N N N N N N N N N N N N N	0	2	н

Compound No.	Х	Y	m	R
5-208	Me HO N Me	0	3	н
5-209	Me Me N N N Me	S	1	Н
5-210	Me Ne No Me	0	1	Ме
5-211	Me Ne No Ne No Ne No Ne No Ne No Ne	0	1	MeO
5-212	Me Me N N N N	0	1	CI
5-213	Me N	0	1	н

Compound No.	X	Y	m	R
5-214	Me N	0	2	н
5-215	Me N N	0	3	н
5-216	Me N	0	4	Н
5-217	Me I N	0	5	н
5-218	Me I N	0	1	MeO
5-219	Me N	0	1	CI
5-220	Me N N	S	1	н
5-221	Me N	s	3	н

Compound No.	X	Y	m	R
5-222	EI N	0	1	н
5-223	D N	S	1	Н
5-224	Pr N	0	1	Н
5-225	Pr-N N	0	1	CI
5-226	Pr N	0	1	н
5-227	₽r N	s	1	н
5-228	Bu N	0	1	н
5-229	Bz N	0	1	н

Compound No.	X	Y	m	R
5-230	Bz N	0	3	н
5-231	Bz N	s	1	н
5-232	Me N	0	1	н
5-233	Et N	0	1	н
5-234	Bz N	0	1	н
5-235	Bz N	S	1	Н
5-236	Me N N Me	0	1	н

Of the compounds isted above, we paticularly prefer the following, theil is to say Compounds No. 1-11, 1-16, 1-18, 1-22, 1-27, 1-49, 1-50, 1-54, 1-58, 1-94, 1-19, 1-104, 1-129, 1-146, 1-155, 1-158, 1-29, 1-29, 1-237, 1-238, 1-247, 1-250, 2-11, 2-49, 2-146, 2-229, 2-237, 2-250, 3-11, 3-49, 3-146, 3-229, 3-237, 3-250, 4-11, 4-49, 4-146, 4-229, 4-237, 4-250, 5-11, 5-49, 5-146, 5-229, 5-237 and 5-250, of which Compounds No. 1-11, 1-16, 1-18, 1-22, 1-27, 1-49, 1-50, 1-58, 1-99, 1-100, 1-109, 1-129, 1-146, 1-229, 1-237, 1-250, 2-11, 2-49, 2-146, 2-229, 2-237, 2-250, 3-11, 3-49, 3-146, 3-229, 3-237 and 3-250 are more preferred. Still more preferred compounds are Compounds No. 1-11, 1-16, 1-27, 1-49, 1-50, 1-54, 1-99, 1-100, 1-109, 1-129, 1-146, 1-229, 1-237, 1-259, and 1-250

The most preferred compounds are Compounds No.:

- 1-11. 5-[4-(1-Methylbenzimidazol-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione;
 - 1-49, 5-[4-(6-Methoxy-1-methylbenzimidazol-2-yl-methoxy)benzyl]thiazolidine-2,4-dione;
 - 1-146. 5-[4-(5-Methoxy-1-methylbenzimidazol-2-yl-methoxy)benzyl]thiazolidine-2,4-dione;
- 1-229. 5-[4-(1-Benzylbenzimidazol-5-ylmethoxy)benzyl]-thiazolidine-2,4-dione;
 - 1-237. 5-[4-(5-Hydroxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione; and
- 20 1-250. 5-[4-(5-Acetoxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione;

and pharmaceutically acceptable salts thereof.

The compounds of the present invention may be prepared by a variety of processes well known in the art for the preparation of compounds of this general type. For example they may be prepared by the following Reaction Schemes 26 A, B, C, D and E:

Reaction Scheme A

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This reaction scheme provides for the preparation of compounds of formula (I) in which Z represents any of the groups of formula (I), (ii), (iii) and (iv), that is to say compounds of formula (Ia).

Reaction Scheme A

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$$X \rightarrow (CH_2)_{m-1} \rightarrow COOR'$$

Step A1

reduction

 $T \rightarrow T$
 $T \rightarrow T$

(III)

(III)

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In the above formulae:

X, Y, R and m are as defined above;

R' represents an allyl group having from 1 to 5 carbon atoms, which may be a straight or branched chain group, for example any finesa allyl groups having from 1 to 5 carbon atoms and included in the examples of groups which may be represented by R* and R* above, and especially a methyl, ethyl or butyl group;

Z' represents a group of formula (i'), (iii'), (iii') or (iv'):

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(in which Ph represents the phenyl group); and

Z* represents a group of formula (i), (ii), (iii) or (iv), as defined above.

Step A1

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In Step A1 of this reaction scheme, a compound of formula (III) is prepared by reducing a compound of formula (II). The reaction is conveniently carried out by reduction using a reducing agent.

There is no particular restriction on the nature of the roducing agents which may be employed in this reaction, and any reducing agent conventionally employed in reactions of this type may equally be employed here. Examples of suitable roducing agents include motal hydridos, such as lithium borohydride, sodium borohydride, sodium cyanoborohydride, include untiminum hydride and dispospopalisminism hydride.

The reaction is normally and preferably affected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that if has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons such as abergrane, tolsenes, yolven, hexane or heptainer, eithers out has deletyle when the trathyrdrotrum or dioxane; amides such as definely without the trathyrdrotrum or dioxane; amides such as dimethyllomamide, dimethylacetamide or hoxamethylphosphoric triamide; alcohols such as methanol, eithenol or isopropend; and mixtures of any two or more of these solvents.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from that of ice cooling to heating, e.g. to the reflux temperature of the reaction medium, preferably with ice cooling or at about room temperature. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents, sepecially the reducing agent, and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 0.5 hour to several days will usually suffice.

The reaction is preferably carried out in an alcohol or in a mixture of one or more alcohols and one or more other organic solvents, in the presence of lithium boorhydride, at a temperature of from room temperature to the reflux temperature of the reaction mixture and for a period of from 1 hourt of 1 day; or in a hydrocarbon or an either in the presence of lithium aluminium hydride or dissolut/valuminium hydride with cooling or heating for a period of from 1 to 0 hours.

Step A2

In Step A2, a compound of formula (V) is prepared by reacting together a compound of formula (III), prepared as described in Step A1, and a compound of formula (IV) using the Misuruhou reaction (D. Misuruhou. Synthesis, 1 (1981)). The reaction is usually carried out in a solvent in the presence of at least one azo compound and at least.

phosphine.

There is no particular restriction on the nature of the azo compounds which may be used, and any azo compounds commonly used in this type of reaction may equally be employed here used. Examples of such azo compounds include diethyl azocidant-loveliberations reliable in the thing to the common the nature.

It is the the property of the common that the property of the p

of the phosphines which may be used, and oxamples include triphonyphosphine and tributyphosphine. The reaction is normally and pretentaby effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can also solve the reagents, at least to some extent. Examples of suitable solvents include: hydrocations, such as benz'ene, follower, sylvene, hazame or heptiane, heliopenated hydrocarbons, such as dinortorm, methylane chloride or 1,2-dichilocoethane; ethers, such as diethyl ethne; tetrahydrofuran or dioxane; amides, such as dimotive formating, dimethylacetamide or hexamethylphosphoric triamide; and mixtures of any two promor of these solvents.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from room temperature to heating, e.g. to the reflux temperature of the reaction mixture, more preferably at a temperature of from room temperature to 60°C. The time required for the reaction may leave the precision of the reaction representative and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several hours to several days, more preferably from 5 hours to 3 days will usually suffice.

25 Step A3

In Step A3, a compound of formula (Ia) is prepared by deprotecting the nitrogen atom in the compound of formula or normula (V). This may be achieved by conventional reactions, for example by treatment with an acid or by catalytic hydrocenation.

Where the reaction is carried out using an acid, there is no perflouler restriction on the nature of the acid which may be used and any acid conventionally used for reactions of this type may equally be used here. Examples of suitable acids include organic, especially carboxylic and suphonic, acids, such as trifluoroacetic acid, trifluoromethanesulphonic acid and seetle acid, and inorganic acids, such as hydrochloric acid and sulphuric acid. The reaction may be carried out in the presence or absence of a solvent.

Where a solvent is used, there is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons, such as benzene, toluene, xylene, hexane or heptane, halogenated hydrocarbons, such as chicordom, methylene othoride or carbon tetrachioride, effects, such as dishertly identified interhydrotruen of downer; amides, such as dimethyliformalick, dimethylecetamide on hexamethylphosphoric triamide; esters, such as eithyl acetate or methyl acetate; water; and mixtures of any two or more of these solvents.

The reaction can take place over a wide ange of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from tex-cooling to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many reflux temperature and the neature of the reactions, notably the reaction temperature and the neature of the reactions and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several tens of minutes to several tens of hours, more preferred by from 0.5 to 10 hours, wite unstally we fulfice.

This step can also be achieved by catalytic hydrogenation of a compound of formula (V). There is no particular restriction on the nature of the catalytes which may be used, and any hydrogenation catalytis commonly used in this type of reaction may equally be employed here. Examples of such hydrogenation catalytis include patiedium-on-charcoal, patietium basick, platinum oxide and platinum back, of which we prefer patietium-on-charcoal.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include hydrocarbons, such as better, followers, visione, better, and the properties of th

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from room temperature to heating, e.g. at the reflux temperature of the reaction mixture, preferably at room temperature or with heating. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several hours to several days, more preferably from 1 hour to 1 day will usually suffice.

Reaction Scheme B

Reaction Scheme B

$$X - (CH_2)_{m} - O - (VI)$$

$$CHO$$

$$Step B2$$

$$O$$

$$NH$$

$$(VIIa)$$

In the above formulae, X, R and m are as defined above.

Step B1

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In Step B1, a compound of formula (VI) is prepared by treating a compound of formula (III) with a base (the first state) and then by reacting the resulting product with a <u>p</u>-fluorobenzalethyrid derivative of formula (VIa), such as 2-methoxy-4-fluorobenzalethyrid error 3-methyrid-4-fluorobenzalethyrid (the second stage).

There is no particular restriction on the nature of the base used in the first stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include hydrides, such as sodium hydride.

The reaction in the first stage is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons, such as benzone, follower, sylven, because or hoppians, others, such as detiryle driven, trainforduran or discounce, amides, such as dimethylformamide, dimethylsoclamide or hoxamethylphosphoric triamide; and mixtures of any two or more of these solvents.

The reaction can take place over a wide range of temperatures, and the procise reaction temperature is not critical to the invention. In general, we find I convenient to carry out the reaction at a temperature of from ice-osciling to healing, e.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many factors, notably the reaction (retignature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several tens of minutes to one day, more preferably from 1 to 10 hours, will busually suffice.

After completion of the first stage reaction, the second stage can be carried out by adding a g-fluorobenzaidehyde derivative of formula (Wa) to the reaction mixture and then by allowing the mixture to react. It is not necessary to separate the reaction product of the first stage before carrying out the second stage.

The reaction of the second stage can take place over a wide range of temperatures, and the precise reaction temperature is not oritical to the invention. In general, we find I convenient to carry out the reaction at a temperature of from room temperature to heating, e.g. to the reflux temperature of the reaction mixture. The time required for the reaction mixes over a wide, depending on many factors, notably the reaction temperature and the nature of the reaction mixes over a wide with the reaction mixed to the reaction in self-action under the preferred conditions outlined above, a period of from several tens of mixed to several daws will usually suffice.

Step B2

35 In Step B2, a compound of formula (VII) is prepared by reacting a compound of formula (VI) with thiazolidine-2.4-dione of formula (VIIa).

The reaction may be carried out in the presence or absence of a catalyst. Where the reaction is carried out in the presence of a catalyst, there is no particular restriction on the nature of the catalyst which may be used, and any catalyst commonly used in this type of reaction may equally be employed here. Examples of such catalysts include sodium acetate, operfulnium acetate and piperfulnium benzoste.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons, such as benzene, followers, xylene, haxane or heptane; eithers, such as diethyl other, tetrahydrofuran or diox-are; alcholes, such as methanol, or handor or isoproport; antides, such as diethyltymaniald, dimethylacetatinde or hexamethylphosphoric triamide; halogenated hydrocarbons, such as methylene chloride, chloroform or 1,2-dichloroethane, nitrities, such as acetonitrile or propionitrile; esters, such as ethyl formate or ethyl acetats; and mixtures of any two or more of these solvents.

The reaction can take place over a wide range of temperatures, and the pricise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction with heating, e.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many factors, notably the reaction imperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 to 50 hours will usually suffice.

The resulting compound of formula (VII) is a compound of the present invention and may be the desired product; alternatively, it may be subjected to optional Step B3.

Step B3

in Step B3, a compound of formula (VIII) is prepared by reducing a compound of formula (VII), preferably by means octably in hydrogenation. There is no particular restriction on the nature of the catalysts which may be used, and any hydrogenation catalysts commonly used in this type of reaction may equally be employed here. Examples of such hydrogenation catalysts include patientium—or hardware and patientium—back, preferably patientium—or hardware coal.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the meation or on the reagents involved and that it can dissolve the reagents at least to some oxtent. Examples of suitable solvents include, hydrocarbons, such as benzene, toluene, xylene, hoxane or heptane; ethers, such as deflarly other, dioxane or tetrahydrotrum; alcohole, such as methanot, ethenol or isopropenal; organic acids, such as formittan acid, acetic acid of propionic acid; anilides such dimethylicmamide, dimethylacetamide or hexamethyliphosphoric triamide; and mixtures of any two or more of these solvents.

The reaction is normally carried out at atmospheric pressure or under superatmospheric pressure; preferably under superatmospheric pressure.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from room temperature or with heating, a.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many factors, noteby the reaction pressure and temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several hours to several days, more preferably from 1 hour to 1 day, will usually suffice.

This step can also be effected by treating the compound of formula (VII) with a metal hydride according to the procedure disclosed in WO 93/1309A.

Reaction Scheme C

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This scheme prepares a compound of formula (I) in which Z is at the para position and is a group of formula (v), that is a compound of formula (X), or in which Z is at the para position and is a group of formula (iv), that is a compound of formula (X).

Reaction Scheme C

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$$X = (CH_2)_m = 0$$

$$CH_2 = 0$$

$$CH_2 = 0$$

$$CH_2 = 0$$

$$CH_2 = 0$$

$$X = (CH_2)_m = 0$$

$$X = 0$$

$$X = (CH_2)_m = 0$$

$$X = 0$$

In the above formula, R, X and m are as defined above.

Step C1

In Step C1, a compound of formula (IX) is prepared by reacting a compound of formula (VI) (which may have been prepared as described in Step B1 of Reaction Scheme B) with hydroxylamine (preferably as the hydrochloride), in a first stage, followed, in a second stage, by reducing the product.

The reaction of the compound of formula (VI) with hydroxylamine (hydrochloride) is, in general, preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least, to some extent. Examples of suitable solvents include: hydrocarbons, which may be a leiphastic or aromatic, such as a benzone, follower, byten, hoxane or hydrane; ethers, such as diethyl other, dioxena or tetrahydroturar; alcohols, such as a methanol, etherol or is coroscendor, andisos, such as diemblyl formanic, dentel vibscendiade or hexamethylospothor.

ic triamide; halogenated hydrocarbons, such as methylene chloride, chloroform or 1,2-dichloroethane; nitriliss, such as acetonitrile or propionitrile, esters, such as ethyl formate or ethyl acetate; amines, such as pyridine, triethylamine or N.N-disporoyi-N-ethylamine, and mixtures of any two or more of these solvents.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from room temperature to heating, e.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary videly, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several hours to severel time of hours will usually suffice.

The subsequent reduction in the second stage of this stop may be certified out by hydrogenation in the presence of a reducing agent. There is no particular restriction on the nature of the reducing agent which may be used, and any reducing agent commonly used in this type of reaction may equally be employed here. Examples of such reducing agents include metal hydrides, such as lithium alturninium hydride, dissolutylatuminium hydride, lithium borohydride, sodium borohydride or sodium quenoborphydride.

The second stage reaction is normally and preferably effected in the presence of a solvent. There is no particular redirection on the nature of the solvent to be employed, provided that it has no adverse effect on the neaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include, hydrocarbons, such as boznons, to Jounes, zylene, havane or heptane, ethers, such as detity either, doxnan or rotrahy-drouters, emides, such as dimethylicomardied, dimethylicotarbons controlled to the solvent of the solvents of the solvents.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of the ine-cooling to heating, e.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several tens of mitutes to one day, more preferably from 1 to 10 hours, will usually suffice.

Step C2

30 In Step C2, a compound of formula (X) is prepared by reacting a compound of formula (IX) with trimethylsilyl isocyanate, of formula Me₃SiNCO (Me represents the methyl group).

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons, such as benzene, followers, hexame or heptame; ethere, such as defetyl ether, dioxame or tetrahydrocarbons, such as what solimetrylomamide, dimetrifly extended not individually carbons, such as methylene chloride, chloroform or 1,2-dichloroethane; and mixtures of any two or more of these solvents.

The reaction can take piace over a wide range of temperatures, and the procise reaction temperature is not critical to the invention. In general, we find to convenient to carry out the reaction at semperature of time ine-cooling to heating, e.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely depending on mary factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several tens of minutes to several days will usually suffice.

The resulting compound of formula (X) is a compound of the present invention. However, if desired, the compound of formula (IX) may be subjected to optional Step C3.

Step C3

In Step C3, a compound of formula (XI) is prepared by reacting a compound of formula (IX) with N-(chlorocarbonyl) isocyanate, of formula CI.CO.NCO.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the neation or or in the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include hydrocarbons, which may be alighatic or aromatic, such as benzene, toluene, xylene, hexane or hepitane; ethers, such as defletyl denty etherlydroturan or document hydrocarbons, such as eximately intermediate, the adjustment of the control of the

these solvents.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical tothe invention. In general, we find it convenient to carry out the reaction at a temperature of the cooling to heating, e.g. to the reflux emperature of the reaction mixture. The time required for the reaction ayals ovary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from several tens of minutes to several tens of hours will usually suffice.

Reaction Scheme D

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This is a process which may be used to prepare compounds of formula (f) in which Z represents a group of formula (ii) or (iii), that is a 2,4-dioxoxitiazolidin-5-yinnethyl or 2,4-dioxoxizzolidin-5-yinnethyl group, i.e. compounds of formula CV/.

Reaction Scheme D

$$\begin{array}{c} \xrightarrow{\text{Step D2}} & \text{X--(CH_2)_{\overline{m}}-Y--} \\ & \text{X} \\ & \text{(XV)} \end{array}$$

In the above formulae:

X, Y, R and m are as defined above;

Y' represents an oxygen or sulphur atom:

Q represents a lower alkoxycarbonyl group, a formyl group, a protected formyl group, a carboxyl group or a hydroxy group; and

Halo represents a halogen atom.

Step D1

In Step D1, a compound of formula (XIV) is prepared by reacting a compound of formula (XII) with a compound of formula (XIII) in the presence of a base

There is no particular restriction on the nature of the base which may be used, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include: nongraine bases, for example of year, hydrides (such as sodium hydride or potassium hydride) and carbonates (such as potassium carbonate or cesium carbonate); and organic bases, such as triethywarine.

The reaction is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the active of the solvent to be employed, provided that it has no advisere effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents includer hydrocations, which may be alightatic or correctlic, such as becare, followers, lydrien, however or heptane; eithers, such as distribly other, fortrahystoriuran or dioxane; amides, such as dimethylformamide, dimethylacetamide or hexamethyphosphotic trainides and mictures of any two or more of these solvents.

The reaction can take place over a wide snage of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at a temperature of from ies-cooling to heating, e.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, the provided that the reaction is effected under the preferred conditions outlined above, a period of from 0.5 hour to several days will usualify suffice.

The reaction is most preferably carried out with cooling or heating or at room temperature in an amide or in a mixture of at least one amide with at least one other organic solvent, in the presence of sodium hydride and for a period of from 1 to 10 hours.

The compounds of formula (XIV), which are prepared by this method, are important intermediates for the preparation of the compounds of formula (I) of the present invention, as well as for the preparation of other valuable compounds. These compounds of formula (XIV) thus also form part of the present invention.

Step D2

In Step D2, a compound of formula (XV) is prepared by one of the following two methods (a) and (b).

Step D2(a)

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The compound of formula (XV) can be produced by reacting a compound of formula (XIV), in which Q represents a lower alkoxycarbonyl group, with a 1,2-diaminobenzene derivative.

a lower standycarcomy group, win a 1,2/calmaniconezane do enterwise.

Wher o I represents a lower alkoxycarbonyl group, this preferably has a total of from 2 to 7 carbon atoms (i.e. the alkoxy part has from 1 to 6 carbon atoms), and may be a straight or branched chain group. Examples of such groups include the methoxycarbonyl, and may be a straight or branched chain group. Examples of such groups include the methoxycarbonyl in-branchycarbonyl, penghosycarbonyl, sepenyltoxycarbonyl, neopenyltoxycarbonyl, 2-methylenyltoxycarbonyl, 1-thyliopxycarbonyl, penghosycarbonyl, sepenyltoxycarbonyl, 1-dembylpenylcoxycarbonyl, 3-dembyltoxycarbonyl, 1-dembylpenylcoxycarbonyl, 1-dembylpenylcoxycarbonyl, 1-dembylbutoxycarbonyl, 1-dembylpenylcoxycarbonyl, 1-dembylbutoxycarbonyl, 1

The reaction is normally and preferably effected in the presence or the absence of a solvent. There is no particular or restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least 10 some extent.

Examples of suitable solvents include: hydrocarbons, preferably aromatic hydrocarbons, such as benzene, toluene or xylene; ethers, such as direthyl ether, tetrahydrofuran or dioxane; amides, such as direthylformamide, direthylgceta-

mide or hexamethylphosphoric triamide; alcohols, such as methanol, ethanol or butanol; acids, such as acetic acid or propionic acid; and mixtures of any two or more of these solvents.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction with heating, e.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 3 hours to several days will usually suffice.

The reaction is most preferably carried out in the absence of a solvent with heating at a temperature of from 50°C to 150°C for a period of from 5 hours to 2 days.

Step D2(b)

As an alternative, the compound of formula (XV) can be produced by reacting a compound of formula (XIV), in which G represents a formly group, in a first stage, with a 1,2-diaminobenzene derivative, and then, in a second stage, treating the product with an oxidizing agent.

The reaction in the first stage is normally and professibly directed in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons, which may be alliphallo or anomatic, such as benzene, toluene, xylene, hexane or heptame; eithers, such as diethyl ether, tetrahydrofuran, downsone or 1,2-dimento, byethera, eithers, such as dismityly dismanified, either dismander or hexametrylyphosphoric triamide, achoroles, such as dismottives of any two or more of these solvents.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at about room temperature or with heating, e.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 1 hour to several daws will usually suffice.

The product is then treated, in the second stage, with an oxidizing agent. There is no particular restriction on the nature of the oxidizing agent which may be used, and any oxidizing agent commonly used in this type of reaction may equally be employed here. Examples of such oxidizing agents include lodine, silver oxide and lead tetrascetate, of which we noter incline.

The freatment with the oxidizing agent in this second stage is normally and preferably effected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents included the solvents clied above for use in the first stage, preferably the ethers.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction with heating. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of fron 1 hour to several days will be usually suffice.

In the compound of formula (XIV), where Q represents a protected formly group, the formly-protecting group may be removed prior to subjecting the compound to the reaction of Slog DQ. Examples of such protected formly groups include. For example, the dimethoxymothyl, diethoxymothyl, 1,3-dioxan-2-yl, 1,3-dioxalan-2-yl, 1,3-diinian-2-yl and 1,3-diinian-2-yl and 1,3-diinian-2-yl and propound of formula (XIV) with a conventional embrack well known in the art, for example by contacting the compound of formula (XIV) with a conventional deprotecting agent under the conditions conventionally used for deprotection, These conditions are described in T. W. Green: Protective Groups in Organic Synthesis (John Willey & Sons Ed.) or J. F. W. McOntrie: Protective Groups in Organic Protective Company in Organic Protective

Reaction Scheme E

This is a process which may be used to prepare compounds of formula (I) in which Z represents a group of formula (ii) or (iii), that is a 2,4-dioxothiazolidin-5-ylmethyl or 2,4-dioxocxazolidin-5-ylmethyl group, i.e. compounds of formula (XV)

Reaction Scheme E

$$X - (CH_2)_m - Y - Q$$
 (XV)
 (XV)
 (XV)
 (XV)

in the above formulae, Q. X, Y, Y', R, R', Halo and m are as defined above;

Step E1

In Step E1, a compound of formula (XVII) is prepared by reacting a compound of formula (XII) with a compound of formula (XVI) in the presence of a base. This reaction is essentially the same as that described in Step D1 of Reaction Scheme D. and may be carried out using the same reagents and reaction conditions.

Step E2

In Sten E2, a compound of formula (XVIII) is prepared by reducing a compound of formula (XVIII).

The reaction may be carried out by a conventional catalytic hydrogenation or by using any reducing agent capable of reducing a nitro group to form an amino group, such as zinc-acetic acid or tin-hydrochior acid. This is a conventional type of reaction and the reaction conditions, solvents etc. which may be employed are well known in the art.

Step E3

In Step E3, a compound of formula (XIX) is prepared by subjecting a compound of formula (XVIII) to a Meenwein arviation reaction.

The conditions employed for the reaction are well known and are generally similar to those disclosed in Japanese Patent Kokai Application No. Sho 55-22657 or reported by S. Oae et al.; Bull. Chem. Soc. Japan, 53, 1065 (1980).

Step E4

In Step E4, a compound of formula (XIV) is prepared by reacting a compound of formula (XIX) with urea or thiourea and then subjecting the product to hydrolysis.

The conditions employed for this reaction are well known and are generally similar to those disclosed in Japanese Patent Kokal Application No. Sho 55-22657.

30 Step E5

In Step E5, a compound of formula (XV) is prepared from the compound (XIV), by one of Steps D(a) and D(b). The reaction is exactly the same as that shown in those Steps and may be carried out using the same reagents and reaction conditions

In the steps described above, the products of each step can, if desired, be recovered from the reaction mixture by conventional means at the end of each reaction and, if necessary, the compounds obtained can be further purified by conventional means, for example, by column chromatography, recrystalization, reprecipitation or similar well known procedures. An example of one such technique comprises: adding a solvent to the reaction mixture, extracting the desired compound; and finally defilling off the solvent from the extract. The residue obtained may be purified by column chromatography through sligics and or like active for ladford the desired compound as a pure sections.

PREPARATION OF STARTING MATERIALS

Reaction Scheme F

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This is a process which may be used to prepare compounds of formula (II) in which X represents a 1-benzimidazolyl group, that is a compound of formula (IIa).

Reaction Scheme F

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In the above formulae:

R', m and Halo are as defined above; and

R" represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms.

The benzimidazole ring in the compounds of formulae (XXXI) and (Ital) may be unsubstituted or it may be substituted any one or more of the 2.4.5.6. and 7- positions by a substituted sected from the group consisting of substituents o, defined and exemplified above. Similarly, the benzene ring of the compound of formula (XXI) may be unsubstituted or it may have from 1 to 4 substituents selected from the group consisting of substituents or, defined and exemplified above. Also, the hydrogen atom shown in the compound of formula (XXI) may be replaced by one of substituents or. Where one or more of substituents is a present in any of the compounds of formulae (XXI), (XXII), (XXII) and (Ital), it is preferably an eight group having from 1 to 4 cations atoms, an any group having from 6 to 10 cation atoms in a carbocyclic ring or an analyl group having for 61 sold of from 7 to 11 cation atoms in the anyl and ality justs; the anyl and analyly aroups may be unsubstituted or they may be substituted, preferably with from 1 to 3 substituents selected from

the group consisting of substituents β, defined and exemplified above.

Where R' represents a lower alkyl group, this may be a straight or branched chain alkyl group having from 1 to 6 carbon atoms. Examples of such groups cludde: the methyl, ethyl, propyl, isopropyl, butyl, socbutyl, sec-butyl, 1-butyl, pentyl, isopentyl, enceptyl, enceptylousyl, 1-ethylpropyl, 4-methylpunyl, 3-ethylpunyl, 2-ethylpunyl, 2-ethylpunyl, 2-dimethylbutyl, 2-3 dimethylbutyl, 2-3 dim

Step F1

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In Step F1, a compound of formula (XXII) is prepared by reacting a compound of formula (XX) with a compound of formula (XXI). This reaction is essentially the same as that described in Step D2 of Reaction Scheme D, and may be carried out using the same reacents and reaction conditions.

15 Step F2

In Step F2, a compound of formula (IIIa) is prepared by condensing a compound of formula (XXIII) with a compound of formula is a wall known type of reaction and may be carried out by well known procedures, for example that described in Liebigs Ann. Chem, 1078 (1984)

Reaction Scheme G

This is a process which may be used to prepare compounds of formula (II) in which X represents a benzimidazole group which is substituted by the group of formula - $(OH_2)_{m-1}$ -COOR' at the 4-, 5-, 6- or 7-position, that is a compound of formula (IIb).

Reaction Scheme G

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In the above formulae, R' and m are as defined above.

The benzimidazolo ring in the compound of formula (III) may be unsubstituted or it may be substituted at from 1 to 5 rithe 1, 2 + 5, 4-5, 6-4 and 7, explained by a walkfullunt elected from the group consisting of substitution is, defined and exemplified above. Similarly, the benzane ring of the compounds of formulae (XXIV), (XXV) and (XXVI) may be unsubstituted or it may have from 1 to 3 substituents selected from the group consisting of substituents as defined and exemplified above [provided that no more than one of the positions of rich or the armine group of the compound of formulae (XXIV) may be so substituted. Also, the hydrogen atom shown in the compound of formula (XXIV) may be replaced by one of substitutes a. Furthermore, the armine group or one of the armine groups of the compounds of formulae (XXIV). (XXVI) and (XXVII) may have a single substituent selected from the group consisting of substituents a, defined and exemplified above. Where one or more of substitutents is present in any of the compounds of formulae (XXIV), (XXVI), (XXVI), and (III), it is preferably an alkyl group having from 1 to 4 carbon atoms, an anyl group having from 5 to 10 carbon atoms in a carbocyclic ring or an aralyle group having thou having a total of from 7 to 11 carbon atoms in the anyl and alkyl parts; the anyl and aralkyl groups may be unsubstituted or they may be substituted, preferably with from 1 to 3 substitutents.

Step G1

In Stop G1, a compound of formula (XXVI) is prepared by nitrating a compound of formula (XXIV). This type of intration reaction is well known and it may be carried out according to the known procedure described by for example:

J. G. Hoggett, R. B. Mocdie, J. R. Peton, K. Schoffeld, Nitration and Aromatic Reactivity, Cambridge University Press,
Cambridge, 1971; K. Schoffeld, Aromatic Nitration, Cambridge University Press, Cambridge, 1980; P. B. D. de la Mare
and J. H. Filed, Aromatic Substitution, Nitration and Halogenation, Association Press, New York, 1959, L. F. Abright in KirkOlimer, Encyleopedia of Chemical Technology, 2nd Vd. 13; The Interscience Enrepcipedad, Inc., New York, 784, 1967; H. A. Lubs, Chemistry of Synthetic Dyes and Pigments, Reinhold Publishing Corp., New York, 1955, pp.
12, 71, 350 etc.

Step G2

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In Step G2, a compound of formula (XXVI) is prepared by reducing a compound of formula (XXV).

There is no particular restriction on the nature of the reducing agent which may be employed in this reaction and any roducing agent commonly used in reactions of this type may equally be employed here. Examples of suitable reducing agents include: a combination of this and hydrochloric acid; zinc and alcoholic alkali; zinc and acetic acid; sodium amalgam and vater; sodium brochydride and tir; and shiller combinations.

The reaction may be conducted in the presence or the absence of a solvent. Where a solvent is employed, there is no particular prestriction on its nature, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons such as bearcano, followen, xylene, behave or helpfares, either seuch as definyl dehe, tetrahydrotrunar or disconse, amidise such as dimethylformamids, dimethylacetamide or hexamethylphosphoric triamide, allochols such as methanol, either or hubanot, estens out as attyl actabilit, water, and mixtures of any two or more of these solvents.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find I convenient to carry out the reactions at atemperature of the reaction includes, a.g. to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on mary factors, notably the reaction integrates and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 0.5 hour to several dave will usually suffice.

This step can also be carried out by catalytic hydrogenation.

There is no particular restriction on the nature of the catalyst which may be employed in this reaction and any catalyst commonly used in reactions of this type may equally be employed here. Examples of suitable catalysts include: Ranay nicksi. Calladium-on-chargoal, calladium-black, ruthenium and platinum oxide.

The reaction is normally and preferably affected in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved and that it can dissolve the reagents, at least to some extent. Examples of suitable solvents include: hydrocarbons such as becare, follower, policy in proceedings of the solvents include: hydrocarbons such as dimethylfromamic, follower, includes such as dimethylfromamic, dimethylsrosemantic or haxamethylfropsphortor triantic, alsohoris such as methanol, ethanol, propanol or ethylene glycot, haboganated hydrocarbons such as chloroform or methylene chloride; water; and mixtures of any two or more of these solvents.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. In general, we find it convenient to carry out the reaction at about room temperature or with healing, a g, to the reflux temperature of the reaction mixture. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from 0.5 hour to several days will usually suffice.

Step G3

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In Step G3, a compound of formula (Itb) is prepared by reacting a compound of formula (XXVI) with a compound of formula (XXI). This reaction is essentially the same as that described in Step D2 of Reaction Scheme D, and may be carried out using the same reagents and reaction conditions.

Reaction Scheme H

The 1,2-diaminobenzene derivative, which is used in Step D2 of Reaction Scheme D and in Step F1 of Reaction

Scheme F, can be prepared by the procedure described in the following reaction scheme H.

Reaction Scheme H

Step H1

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In Step H1, a compound of formula (XXVIII) is prepared by nitrating a compound of formula (XXVII). This reaction is essentially the same as that described in Step G1 of Reaction Scheme G, and may be carried out using the same reagents and reaction conditions.

Step H2

In Step H2, a compound of formula (XX) is prepared by reducing a compound of formula (XXVIII). This reaction is sessentially the same as that described in Step G2 of Reaction Scheme G, and may be carried out using the same reacents and reaction conditions.

BIOLOGICAL ACTIVITY

The compounds of formula (i) and salts thereof possess the ability to reduce insulin resistance, hyperipicaemia, gestational diabetes malitus, obesity, impaired glucose tolerance, diabetic complications, artriosciarosis, cataracts, and polycystic owary syndrome, and, in addition, have ablose reductase inhibitory activity, 5-lipoxygonasci inhibitory activity and the ability to inhibit the formation of lipid peroxico. They are thus useful for the prevention and/or therapy of hyperipiciaems, hypergylcaemia, doestly, impaired glucose tolerance, hypertension, osteoporosis, cachexia, fatty liver, diabetic complications, arteriosclerosis, and cataracts, for the prevention and/or therapy of other diseases caused by insulin resistance, including gestational diabetes mellitus, and polycystic oway syndroms; and for the prevention and/or therapy of inflammatory diseases, acno, surbourn, psoriasis, oczama, allergic diseases, asthma, Glulucc, cardiovacoutar diseases, afterosclerosis, and cellular injury induced by isotherine diseases.

The compounds of the present invention can be administered in various forms, depending on the disorder to be treated and the age, condition and body weight of the patient, as is well known in the art. For example, where the compounds are to be administered orally, they may be formulated as tables, capsules, granules, powders or syrups; or for parenteral administration, they may be formulated as injections (intravenous, intramuscular or subcutaneous), drop infusion preparations or suppositionis. For application by the ophthalmic mucuous membrane route, they may be formulated as eyedge or or eye orintmats. Those formulations can be prepared by conventional means, and, if desired,

the active ingredient may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent or a coating agent.

Examples of vehicles which may be employed include, organic vehicles including, sugar derivatives, such as laces, sucreae, glucose, marnical and sorbifets starte diversitiens, such as care lasterb, beaterin and carboxymethylstarch; cellulose derivatives, such as crystalline cellulose, low-substituted hydroxypropyicallulose, carboxymethyleolulose, carboxymethyleolulose, carboxymethyleolulose, developed income carboxymethyleolulose, granteric d

Examples of lubricants which may be employed include: steeric acid, metal steerates, such as calcium steerate and mangeeium steerate; talc; colloidal silica; waxes, such as bee gum and spermaceti wax; boric acid; adipic acid; sulphrates, such as sodium sulphrate; plycof, trunaric acid; sodium benzoate; <u>DL</u> teocime; fathy acid sodium salls; lauyi sulphrates, such as sodium sulphrate; sulphrates, such as solicic anhydride and silicic acid hydrate; and the adorementioned starch destruitives.

Examples of binders which may be employed include; polyvinylpyrrolidone; macrogol; and the same compounds as are mentioned above for the vehicles.

Examples of disintegrators which may be employed include; the same compounds as are mentioned above for the vehicles; and chemically modified starches and celluloses, such as sodium crosscarmellose, sodium carboxymethvistarch and bridged polyvinyrolidone.

Examples of stabilizers which may be employed include: paraoxylebnazoates, such as methylparabene and propyl-parabene; alcohols, such as chiorobutanol, benzylatohol and phenylethylalchol; benzalkonium chloride; phenols, such as phenol and cresol; thimmersal; dolytdroacetic acid; and sorbiota acid.

Examples of corrigents which may be employed include: sweetening agents, acidifiers and spices.

Although the dosage will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the discorder to be teaded or prevented, the route of administration and the form of the drug, in general, where the drug to to be administered craitly, a daily dosage ranging from a minimum of 0.0 fing (preferally 1 mg) to a maximum of 200 mg (preferally 500 mg and more preferably 10 mg) or go the compound is recommended for an abult human patient, and this may be administered in a single dose or in divided doses. Where the drug to be administered in a single dose or in divided doses. Where the drug to be administered in a single dose or in divided doses. Where the drug to be administered in a single dose or in divided doses. Where the drug to be administered or introvercusty, a daily dosage ranging from a minimum of 0.01 mg (preferably 0.1 mg) to a maximum of 500 mg (preferably 0.1 mg) to a mg (preferably 0.1 mg

The activity of the compounds of the present invention is illustrated by the following Experiments.

Experiment 1

Hypoglycaemic activity

The lest animals used wore hyperglycamic male mice of the KK strain, each having a body weight of at least 40. The compounds under test were mixed with a 1: by oclume mixture of polyethyloane glycol 400 and water. Each animal was orally administered a test compound in the amount shown in the following Table 6 and then allowed to feed relegif or 16 hours. At the end of this time, blood was collected from the rails viers without enset thesis. The blood glucose level (GGL) was determined by means of a glucose analyzer (GL-101, manufactured by Mitsublishi Kasei Co. or a Glucordore-F amurfactured by Mitsublishi Casei Co. or a

The hypoglycaemic effect was calculated by the following equation:

Hypoglycaernic effect (%) =

[(BGL, - BGL,)/BGL,] x 100

where:

BGL, is the blood glucose level in the group administered a solvent only, but no active compound; and

8 BGL, is the blood glucose level in the group administered a test compound.

The results are shown in the following Table 6, in which each compound of the present invention is identified by the number of one of the following Examples in which its preparation is illustrated.

Table 6

Cpd. of Example No.	Dose (mg/kg)	Hypoglycaemic effect (%)
1	1	36.2
2	1	27.2
3	1	11.2
4	1	19.3

As is apparent from Table 6, the compounds of the present invention exhibited excellent activity.

Experiment 2

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Inhibition of Aldose reductase

Bowine lens alclose reductase was separated and partially purified by the method of S. Hyman and J. H. Kincehlte J. Biol. Chem., 240, 877 (1965)) and K. Inagaki, I. Miwa and J. Okuda (Arch. Biochem. Biophys, 216, 337 (1962)), and its activity was obtamined photometrically by the method of Varma at al. [Biochem. Pharmac, 25, 2505 (1976)]. Inhibition of enzyme activity was measured for the compounds of the present invention at a concentration of 5 µg/m1, and the measured values were used to calculate the IC₆₀ values. The results are shown in the following Table 7.

Table 7

Cpd. of Example No.	Inhibition (%) at 5 µg/ml	IC ₅₀ (μg/ml)
1	80.3	0.77
3	79.6	1.40

Experiment 3

30 Toxicity

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The toxicity of the compounds of the present invention was tested on male F344 rats, divided into groups of 5. The test compound was administered orally to each test animal at a dose of 50 mg/kg of body weight per day for 2 weeks. The test compounds used were those of Examples 1 and 2. The animals were observed for 2 successive weeks, and, during that period, they showed no ebnormalities which could be attributed to the test coumpounds. In view of the substantial dose administered to each animal, the zero mortality rate indicates that the compounds of the present invention have very low toxicity.

The compounds of the present invention thus have excellent activities combined with a very low toxicity, rendering them ideally suited to the accuracy to the combined with a very low toxicity, rendering

The present invention is further illustrated by the following non-limiting Examples. In these Examples, where Compound Nos, are given, they are those numbers assigned in the foregoing Tables 1 to 5. Preparation of certain of the starting materials used in some of these Examples is illustrated by the subsequent Proparations. Preparation of certain compositions which may be made containing the compounds of the invention is illustrated by the subsequent Formulations.

EXAMPLE 1

5-[4-(1-Methylbenzimidazol-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione (Compound No. 1-11)

A mixture of 1.0 g of X-methyl-1,2-phenylenediamine, 3.8 g of 5.4(-othoxycarbonylmethoxylphenzyl]hiazolidine-2,4-dione (prepared as described in Preparation 4), 20 ml of concentrated aqueous hydrochloric acid, 10 ml of 1,4-dioxane and 10 ml of water was heated under reflux for 5 hours. At the end of this time, the insoluble materials which had precipitated from the reaction mixture were collected by filtration and the precipitate thus obtained was dissolved in tetrahydrotrum. Water was then added to the solution. The resulting aqueous mixture was neutralized by adding sodium hydrogencurbonate and then extracted with ethyl acetate. The extract was washed with an aqueous solution of sodium chloride and direct over arrhydrous sodium sulphata. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was quilled by column chromatography frough silica gel using ethyl

acetate and then ethanol as the eluent. The product was then recrystallized twice from a mixture of tetrahydrofuran and ethyl acetate, to give 1.3 g of the title compound, melting at 230 - 231°C.

EXAMPLE 2

5-[4-(6-Methoxy-1-methylbenzimidazol-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione (Compound No. 1-49)

A mixture of 21.8 g of 5-methoxy-N-methy-1.2-phenylenediamine (prepared as described in Proparation 9), 83.4 g of 5-(4-methoxocarbonylmehoxybenzyl)-thiszolidin-2.4-done (prepared as described in Proparation 21), 250 ml of 1,4-dioxane and 750 ml of concentrated aqueous hydrochloric acid was heated under reflux for 60 hours. At the end of this time, the reaction mixture was cooled with ice, after which the solid matter was collected by filtration. 500 ml of 5% w/v aqueous solution of solom hydrogenezabronate was added to this matter, and the resulting mixture was stirred at room temporature for 2 hours. Insoluble materials were then collected by filtration and dissolved in a mixture of 1000 ml of dimethyl floremarride and 200 ml of methanol. The resulting solution was discolorized by treatment with activated charcosi, which was then removed by filtration. The filtrate was then concentrated by evaporation under reduced pressure to a volume of about 55 ml. The resulting concentrate was added to 750 ml of delityl effort and the solution thus obtained was allowed to stand for 2 days. At the end of this time, the resulting procipitate was collected by filtration, to give 20.1 g of the title compound, melting at 267 - 271°C and having an Rf Vaule a 0.88 (on thin layer chromatography on silics, age; using a developing abovent of methylone choicide containing 55% v/v ethanols.

EXAMPLE 3

5-[4-(5-Hydroxy-1,4,6,7-tetramethylbenzimidazol-2-yl-methoxy)benzyllthiazolidine-2,4-dione (Compound No. 1-237)

A mixture of 1.0 g of 4-sectoxy-½-methy/3.5,6-trimethy/1.2-phenytonediamine (prepared as described in Proparation 13), 2.7 g of 5-(4-methoxycarbonytimethoxychemythhatoxidine-2.4-denoe (prepared as described in Proparation 21), 5 mil of 1,4-dioxana and 25 mil of concentrated aqueous hydrochloric acid vias heated under reflux for 2 days. At the end of this time, the reaction mixture was action to its country hydrogenacomate. It was then extracted with entry acetate, mixture was neutralized by the addition of socialize mydrogenacomate. It was then extracted any extension mydrogenacomate with a saturated aqueous solution of socialized pressure, after which the residue was suprified by column chromatography through sitica get, using einhy acetate as the eluent. Fractions containing the title compound were collocted and the solvent was then was removed by distillation under reduced pressure, to give are of residual oil. 150 mil of lightly ether were added to the oil, and the mixture was agitated ultrasonically for 5 minutes. The precipitate which separated out was collected by filtration and dissolved in 300 mil of tetrally/circlumn. The resulting solution was concentrated to a volume of between aboul 10 mil and 20 ml by evaporation under reduced pressure, 200 mil of ethyl acetate were added to the concentrate, and the mixture was agilated ultrasonically for 20 minutes. The precipitate which separated out was collected by filtration, of one 9.52 g of the title compound, melting at 240 - 244°C and having an Ri value = 0.44 (on thin layer chromatography on silica set developing solvent ethyl acetate.)

EXAMPLE 4

5-[4-(5-Hydroxy-1,4,6,7-tetramethylbenzimidazol-2-vlmethoxy)benzv|]thlazolidine-2,4-dione hydrochloride (Hydrochloride of Compound No, 1-237)

A suspension of 0.12 g of 544-(5-hydrony-1.46,7-letramethybenz/mickzol-2-ymentoxy)plenz/liphiazoliding-2-4-dione (prepared as described in Exemple 3) in 3 ml of a 4 N solution of hydrogen chloride in ethyl acetale was stirred for 3 hours at room temperature, after which it was allowed to stand overnight. Insoluble substances were collected by filtration and washed with letrahydrofusan, with ethyl acetale and with deithyl other, in that order, to give 0.11 a of the title compound, molting at 228 - 231" as

EXAMPLE 5

5-[4-(5-Acetoxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (Compound No. 1-250)

0.032 ml of acetic anhydride were added at room temperature to a solution of 0.12 g of 544(5-hydroxy-1.4,6,7-te-tramethylbenzimidazoi-2-yfmethoxyjbenzyjl-thiazoidine-2.4-dione (prepared as described in Example 3) in 2 ml of pylidine, and the resulting mixture was stirred for 3 hours, after which it was allowed to stand overnight. At the end of

this time, the reaction mixture was freed from the solvent by evaporation under reduced pressure, and the resulting residue was mixed with water. The approxes mixture was then extracted with only actionate. The extract these was the with water and then with a saturated acqueous solution of sodium chloride and dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure, after which the solid residue was triturated with distryl ether and collected by filtration. It was then washed with diethyl ether, to give 0.12 g of the title compound, meltin as 1250 - 255°C.

EXAMPLE 6

5-[4-(5-Methoxy-1-methylbenzimidazol-2-ylmethoxy)-benzyllthiazolidine-2,4-dione (Compound No. 1-146)

A mixture of 1.17 g of 4-meithoxy-N-meithyl-1.2 phenylenediamine (prepared as described in Preparation 25), 30 of 5-(4-meithoxy-arbonylmethoxy)benzyl)-hiszoiclidne-2,4-dione (prepared as described in Preparation 21), 20 ml of 1,4-dioxana and 50 ml of concentrated hydrochloric acid was heated under reflux for 2 days. At the end of this time, the reaction mixture was poured into ice-water and the resulting mixture was neutralized with sodium hydrogencarbonate, after which it was oxtracted with only aceted. The extract was washed with a suburated aquoons solution of sodium-hibride and dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, after which the residue was purified by column chromatography through silica gel, using a solution of methylene chioride containing 3% by volume ethanol as the eluent, to give 0.3 g of the title compound, meiting at 209 - 210°C and having an Ri value = 0.56 (on thin layer chromatography on silica get, developing solvent: methylene chioride containing 3% by volume ethanol.

EXAMPLE 7

5[-4-(1-Benzylbenzimidazol-5-ylmethoxy)benzyll-thiazolidine-2,4-dione hemihydrate (Hemihydrate of Compound No. 1-229)

A mixture of 0.26 g of 5-14-(1-benzy/benzymi-dazol-5-ymethoxy/benzy/l-3-tripheny/methythiazolidin-e2-4-dione (prepared as described in Proparation 29), and a seetis caid and 1 not water was sirred of 3 hours at 50°C in oil beth. At the end of this time, the reaction mixture was neutralized with sodium hydrogencarbonate and then extracted with ethyl acotate. The extract was washed with a saturated aqueous solution of sodium chloride and dried over any hydrous sodium sulphate. The solvent was then removed by evaporation under reduced pressure, and the resulting residue was recrystallized from a mixture of ethanol and methanol, to give 116 mg of the title compound; melting at 185 - 187°C.

PREPARATION 1

Methyl 4-nitrophenoxyacetate

A mixture of 56 g of 4-nitrophenot, 90 g of methyl bromacectate, 100 g of potassium carbonate and 500 ml of dimethylformanie was stirred at room temperature for 2 days. At the end of this time, he solvent was removed by distillation under reduced pressure. The resulting residue was mixed with water and the aqueous mixture was extracted with othyl accutact. The oxfract was washed with water and dried over anhytrous souldim sulphato, after which the solvent was removed by distillation under reduced pressure. The resulting residue was triturated with hoxane to give 8.3 a of the tile compound, mellina at 98 - 990°C.

PREPARATION 2

Methyl 4-aminophenoxyacetate

A solution of 30.8 g of methyl 4-nitrophenoxyscetal (preparad as described in Preparation 1) in 500 m lof methanol was shaken in an atmosphere of hydrogen and in the presence of 5.0 g of 10% why palladium-on-charcoal for 6 hours. At the end of this time, the reaction mixture was filtered and the filtrate was concentrated by evaporation under reduced pressure, to give 25 8 g of the title compound having an Rt value = 0.79 (on thin layer chromatography on silica get, developing solvent: of that deatate).

PREPARATION 3

Methyl 4-(2-bromo-2-butoxycarbonylethyl-1-yl)-phenoxyacetate

98 g of 47% wW aujeouis hydrobromic acid, followed by 33 ml of an aqueous solution containing 12 8 g of socium nitritie, were added to a solution of 25 8 g of methyl 4-aminophenosycaetate (repeared as described in Preparation 2) in 253 ml of a 2 : 5 by volume mixture of methanol and acetone, whilst be-cooling, and the resulting mixture was stirred, whilst be-cooling, 5 or 30 minutes. 18 2 g of buyl acrylate were then added, and the resulting mixture was stirred for a further 30 minutes, whilst be-cooling, 3 2 g of coppelf) bornoids were then added to the mature, and the resulting was stirred for a stirred for a mixture was stirred overnight at room temperature. At the end of this time, the reaction mixture was freed from the solvent by distillation under reduced pressure, and the residue was mixted with an aqueous solution of sodium chloride. It was then extracted with ethyl acetate. The extract was washed with an aqueous solution of sodium chloride and dried over enhydrous sodium sulphate. On distilling of the solvent, there were obtained 517 g of the title compound having an Fit value = 0.48 (on this layer chromatography on silica get, developing solvent: a 5: 1 by volume mixture of hexane and third sectate) as a crude product.

PREPARATION 4

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5-[4-(Ethoxycarbonylmethoxy)benzyl]thiazolidine-2,4-dione

A mixture of 100 g of of methyl 4-(2-bromo-2-butoxycarbonylethyl-1-yl)phenoxyacetate (prepared as described in Preparation 3); 2 g of thourse and 200 ml of ethanol was headed under reflux for 2-5 hours, after which 2 N aqueous hydrochloric acid was added to the reaction mixture. The mixture was then heated under reflux for 5-hours. At the end of this time, the reaction mixture was freed from the solvent by distillation under reflux pressure. The resulting residue was diluted with water and the aqueous mixture was extracted with eithyl acetate. The extract was dired over anhydrous magnesium sulphate, after which the solvent was removed by distillation under reduced pressure. The resulting residue was purified by column chromatography through silics gel using a 2: 5 by volume mixture of ethyl acetate and hexane as the eluent, to give 19.4 g of the title compound, melting at 105 - 106°C.

30 PREPARATION 5

5-Methoxy-2-nitroaniline

70 ml of a 25% w/v methanolic solution of sodium methoxido were added at corn temperature to a solution of 25 of 5-chior-2-nitroeniline in 500 ml of 1,4-dioxane, and the resulting mixture was heated under reflux for 4 hours, after which the solvent was removed by distillation under reduced pressure. The resulting residue was diluted with water, and the resulting residue was diluted with water, and the resulting aqueous indure was oxtracted with orityl acetate. The extract was washed with a saturated aqueous solution of sodium choirels and dried over enhydrous sodium subpleat, after which the solvent was removed by distillation under reduced pressure. The resulting residue was purified by column chromatography through silica gel using a gradient elution method, with mixtures of ethyl acetate and hexare in ratios ranging from 1: 4 to 1: 2 by volume as the eluent, to give 16.3 go 1 the title compound, mething at 124 - 128°C.

PREPARATION 6

N-t-Butoxycarbonyl-5-methoxy-2-nitroaniline

25 g of di-buly (dicarbonate, 15 ml of pyridine and 0.6 g of 4-dimethylaminopyridine were added at room temperature to a solution of 16 g of 5-methory2-introcatining (repeared as described in Preparation 5) in 500 ml of dehydrate testalysicifuran, and the resulting mixture was sirred for 2 hours. At the end of this time, the reaction mixture was fread from the solvent by distillation under roduced pressure, and the resulting esqueuus mixture was extracted with drifty activate. The oxfract was washed with a saturated aqueous solution of socium children and resulting activated with the solvent was removed by distillation under reduced pressure. The resulting resultine was purified by column chromatography through sitilica glue using a 11 : 10 by volume mixture of shifty activated and excess as the elution, to over 125 g of the tilte compound, mediging at 112 : 1145 °C.

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PREPARATION 7

N-t-Butoxycarbonyl-N-methyl-5-methoxy-2-nitroaniline

A solution of 48 6 of M-t-butdoycenbonyl-5-methoxy2-pintronnine (prepared as described in Proparation 6) in 300 ml of dehydrated dimethylfromamide was added, whilst lice-occling, to a suspension of 12.0 g of solution hydride (as a 55% who dispersion in mineral oil) in 300 ml of dehydrated dimethylfromamide, and the resulting mixture was stirred of 100 minutes, after which 172 ml of methyl lodded were added at room temperature. The reaction mixture was stirred for 1 hour, after which it was allowed to stand overnight at room temperature. It was then concentrated to about one-lifth of its original volume by avaporation under reduced pressure. The concentrate was mixted with low-active rewater and the resulting aqueous mixture was extracted with eithyl activation. The extract was wested with water and with a saturated aqueous solution of sodium chloride, in that crofe, rater which it was dried over anhydrous sodium sulphafet. On distilling of the solvent, there were obtained 52 if g of the title compound, melting at 122-144°C.

6 PREPARATION 8

N-Methyl-5-methoxy-2-nitroaniline

750 ml of a A N southor of hydrogen chloride in 1,4-dioxane were added to 52 g of N4-butoxycsrbony/-N-msthy/-Smethyxy-Chrocalline (prepared as described in Preparation 7) a from temperature, and the resulting mixture was stirred for 2 hours. At the end of this time, the reaction mixture was freed from the solvent by distillation under reduced pressure, and the resulting residue was mixed with valer and ethyl acatale. The mixture was then neutralized by the addition of sodium hydrogencationale, after which it was extracted with eithyl acatale. The extract was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulphate. On distilling off the solvent, there were obtained 55.8 g of the title compound, melting at 107 - 110°C.

PREPARATION 9

5-Methoxy-N-methyl-1,2-phenylenediamine

A45 g of stancous chloride were added to a mixture of 35 g of N-melhy5-meltrony2-nitronalline (prepared as described in Preparation 8), 900 ml of 1-butanol and 100 ml of athy1 acetate at room temperature, and the resulting mixture was stirred at 80°C for 2 hours, after which 11 g of sodium borohydride were added in portions at 80°C over a period of about 1 hour. The reaction mixture was then stirred at 80°C for 3 hours, after which twis allowed to start a room temperature for 2 days. It was then poured into loc-water and the aqueous mixture was neturalized by the addition of sodium hydrogenearbonate. The mixture was extracted with ethy1 acetate, and the extract was washed with a saturated aqueous solution of sodium chloride and dried over anhyticus sodium subjets. The solvent was removed from the mixture by distillation under reduced pressure, and the resulting residue was purified by column chromatography through allica gel using a 31 c. 2 by volume mixture of eithy1 acetate and hoxane as the eluent, to give 21.9 g of the title compound having an RI value = 0.18 (on thin layer chromatography on sitica get, developing solvent a 1:1 by volume mixture of eithy1 acetate and hoxane.)

PREPARATION 10

5 Trimethylbenzoquinone

A suspension of 25.6 g of fortic chloride in 50 ml of water was added at room temperature to a solution of 20 g of intentlyinjydroujnone in 150 ml deaction, and the resulting mixture was stirred for 1 hour, after which it was allowed to stand for 2 days. At the end of this time, it was concentrated to about one half of its original volume, and the contract was mixed with water. The resulting aqueous solution of sodium chloride, in that order, after which it was dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure, and the resulting residue was purified by column chromatography through sitilia gal, using a 1: 6 by volume mixture of eithy acetate and hexan e as the eluent, to give 16.9 g of the title compound having an Rif value = 0.48 (on this layer chromatography on sitica agi, developing solvent; a 1: 6 by volume mixture of eithy acetate and hexans.)

PREPARATION 11

2,3,6-Trimethylbenzoquinone-4-oxime

A solution of 7.04 gof hydroxylamine hydrochloride in 30 ml of water was added at room temperature to a solution of 16.9 gof trimethylbenzoquinone (prepared as described in Preparation 10) in 150 ml of methanol, and the resulting mixture was stirred for 2 hours, atter which it was allowed to stand for 2 days. At the end of this time, the reaction mixture was diluted with 1000 ml of water. The precipitate which separated out was collected by filtration and recrystalized from a mixture of eithyl acute and a not expense. In give 112 gof the title compound, mething at 183 = 190°C.

PREPARATION 12

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4-Hydroxy-2.3.5-trimethylaniline

15/2 g of sodium hydrosulphile were added, whilst be-cooling, to a mixture of 38.15 g of 2.9.4-trimethylbenzoquinons-4-oxime (prepared as described in Preparation 11) and 880 ml of a 1 N aqueous oscilland of sodium hydroxide, and the resulting mixture was stirred at room temperature for 1 hour, after which it was allowed to stand overnight. The reaction mixture was then pound into its eventer and the pl of the aqueous mixture was adjusted to a value of 4 to 5 by the addition of 5 N aqueous hydrochoric sod, after which it was neutralized with sodium hydrogenocratic The mixture thus obtained was extracted with eithyl acetate. The extract was washed with a saturated aqueous solution of sodium chioride and died over anhydrous sodium usphilate. The solvent was then removed by distillation under reduced pressure, after which the crystalline residue was triturated with diisopropyl either and collected by filtration. On washing with diisopromyl either, there were obtained 30.1 or 10 the title compound, meltin at 131 in 134°C.

25 PREPARATION 13

N-t-Butoxycarbonyl-4-hydroxy-2,3,5-trimethylaniline

22.0 ml of triethylamine were added at room temperature to a solution of 20 g of 4+tydroxy-2,3,5-trimethylamine (propared as described in Preparation 12) in 500 ml of tetrahydrofuran, followed by 34.6 g of dit-butyl dicarbonate, and the resulting mixture was streaf for hours, after which it was allowed to stand overight. At the end of this time, the reaction mixture was freed from the solvent by distillation under reduced pressure, and the resulting residue was mixed with water. The resulting aqueous mixture was extracted with ethyl acetate. The extract was washed with a saturated aqueous solution of scolum chloride and dried over anhydrous sodium sulphate. The solvent was removed by distillation under reduced pressure, after which the crystalline residue was triturated with hexane, to give 31.9 g of the title comound, melting at 158 - 161°C.

PREPARATION 14

40 N-Methyl-4-hydroxy-2,3,5-trimethylaniline

A solution of 15 g of N-t-butoxycarbonyl-4-hydroxy-2.3,4-timenthylamiline (prepared as described in Preparation 3) in 200 mil of dehydrated textra/hydrotura was exided to a suspension of 6.8 g of thirm alternium hydride in 300 mil of dehydrated textra-hydroturan, whilst is-excelling, and the resulting mixture was stirred at room temperature for 3 hours, after which it was heated under reflux for 2 hours. After end of 10 this time, a mixture of 10 mil of vater and 30 mil of textra-hydrofuran was added to the reaction mixture in order to destroy any excess of lithium alternium hydride. The reaction mixture was then stirred at room temperature for 1.5 hours, after which insoluble materials were filtered of with the aid of a Ceilite (trade mark) filter aid. These materials were washed with ethyl accetate, and the ethyl accetate washings were combined and died over anhydrous sodium subplast. The solvent was removed by distillation under reduced pressure, and the resulting residue was purified by column chromatography through sities get using a 1.3 by volume mixture of sthyl accetate and housens as the elevent, or give 51 of the title compound, melting at 120 122°C.

PREPARATION 15

N-t-Butoxycarbonyl-N-methyl-4-hydroxy-2,3,5-trimethylaniline

5.0 ml of triethylamine and a solution of 7.92 g of di-t-butyl dicarbonate in 30 ml of tetrahydrofuran were added at room temperature to a solution of 5.0 g of N-methyl-4-hydroxy-2,3,5-trimethylaniline (prepared as described in Prep-

aration 14) in 70 ml of tetrahydrofuran, and the resulting mixture was stirred for 1 hour, after which it was allowed to stand overright. All the end of this time, the reaction mixture was record from the solvent by distillation under reduced pressure, and the resulting residue was mixed with water. The equous mixture was extracted with eithyl acetallar. The extract was washed with water and vitin a saturated aqueous exhibition of sodium chloride, in that order, after which it was dried over anhydrous magnesium sulphate. After distilling off the solvent, he residual crystals were triturated with hexane and collected by filtrition. There were obtained 7.55 g of the title compound, mothing at 163.1694.

PREPARATION 16

N-I-Butoxycarbonyl-N-methyl-4-acetoxy-2,3,5-trimethylaniline

5.64 m of dehydrated triethylamine and 2.9 m of acetyl chioride were added at room temperature to a solution of 2.9 of Nt-butoxycarbonyl-Y-methyl-4-hydroxy-2.3.5-trimethylamiline (prepared as described in Preparation 15) in 100 ml of dehydrated tetrahydroturan, and the resulting mixture was stirred for 1 hour, after which it was allowed to stand owenight. The reaction mixture was then diluted with water and the aqueous mixture was extracted with ethyl acetate. The extract was washed with water of and with a saturated aqueous solution of sodium chloride, in that crote, after which it was dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure, after which the residue was trituted with ite-coded hoxane to cause crystalization. The crystals were collected by fifterion and washed with ise-coded hexane to give 6.55 g of the title compound, mething at 103-104°C.

PREPARATION 17

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N-Methyl-4-acetoxy-2.3.5-trimethylaniline hydrochloride

A mixture prepared by adding 100 ml of a 4 N solution of hydrogen chlorids in 1.4-dioxane to 5.45 g of N½-butox, verbornyl½-methyl4-actoxyz, 25-frimethylaninin (prepared as described in Preparation 15) at room imperature was stirred for 3 hours. At the end of this time, the reaction mixture was freed from the solvent by distillation under reduced pressure, and the resulting resizive was intrusted with discoppopyl effect. The crystals thus obtained were collected by fiftration, after which they were washed with discopropyl ether to give 4.38 g of the title compound, melting at 172-178°C.

PREPARATION 18

N-Methyl-4-acetoxy-2,3,5-trimethyl-6-nitroaniline

4.3 g of N-methyl-4-acetoxy-2,3.5-trimethylaniline hydrochloride (prepared as described in Preparation 17) were added to ice-cooled concentrated aqueous nitric acid, and the resulting mixture was stirred, whilst ice-cooling, for 10 minutes and then at room temperature for 10 minutes. At the end of this time, the reaction mixture was poured into ice-water and the aqueous mixture was neutralized by the addition of sodium hydrogen-carbonate, after which it was extracted with rethy acetate. The extract was washed with a saturated aqueous solution of sodium cholde and dried over anhydrous sodium sulphate. The solvent was then removed by distillation under reduced pressure, after which 5 ml of discopropyl ether and 50 ml of hexane were added to the residue. The mixture was then agilited thirdsonically for 5 minutes. Insoluble pracipitates were triturated with a 1:1 by volume mixture of discopropyl ether and hexane. The resulting crystals were collected by fittration, after which they were washed with a 1:1 by volume mixture of discopropyl ether and hexane to give 2.76 g of the title compount, melting at 143:146.

PREPARATION 19

4-Acetoxy-N-methyl-3,5,6-trimethyl-1,2-phenylenediamine

A solution of 2.65 g of y-mothyl-4-acotoxy-2.5-trimethyl-6-nitroanline (prepared as described in Properation 19) in a mixture of 20 in thehanol and 20 in of ehryl acototh was shaken at room temperature for 3.5 hours and then at 40°C for 3 hours in an atmosphere of hydrogen and in the presence of 0.2 g of plainium oxide. At the end of this time, the reaction mixture was filtered to remove the plainium oxide and the filterate was read from the solven try distillation under roduced pressure. The resulting residue was purified by column chromatography through alika get, using at 1 by volume mixture of shyl acotate and hexane as the elevant, to give 1.3 got fills compound, melting at 113 - 116°C.

PREPARATION 20

5-(4-Methoxycarbonylmethoxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione

128 gof cesium cathonate were added at room temperature to a solution of 120 gof 5-(4-hydroxyberxyh)-3-triphenyhmethythiszolidine-2,4-dione in 2.5 litres of acetone, followed by 36 ml of methyl bromosectate, and the resulting mixture was stirred for 1 hour. At the end of this time, the reaction mixture was there from the solvent by distillation under reduced pressure, and the resulting residue was mixed with vestor. The acqueous mixture was then extracted with orbity acetals. The extract was washed with water and then with a salturated acqueous solution of sodium chloride, after which it was dried over anhydrous magnesium sulphate. The solvent was removed by distillation under reduced pressure, after which I filter of delithyl either was added to the oily residue. The mixture was then agitted utilizationally for 10 mixtures. The solid substance precipitated was collected by filtration, to give 126.3 gof the title compound, meiting at 156.1 ABCV.

5 PREPARATION 21

5-(4-Methoxycarbonylmethoxybenzyl)thiazolidine-2,4-dione

1700 ml of acetic acid and then 400 ml of water were acided at room temperature to a suspension of 344 g of 5-4-methoxycarbony/methoxybenzyl/3-dripheny/methylthiazoidine-2.4-drion (progrand as described in Preparation 20) in 400 ml of 1.4-dioxane and the resulting mixture was stirred for 5 hours at 80°C. At the end of this time, the reaction mixture was freed from the solvent by evaporation under reduced pressure, and the resulting residue was purified by column chromatography through silica gal using a 1 : 2 by volume mixture of ethyl acetate and hexane, a 2 : 1 by volume mixture of ethyl acetate and hexane and then ethyl acetate as eluents, to give 161.7 g of the title compound, mellion at 100 - 106°C.

PREPARATION 22

N-t-Butoxycarbonyl-4-methoxy-2-nitroaniline

A solution of 2.5 g of 4-metrony-2-nitroniline in 30 mt of dehydrated dimethyformarride was added at room temperature to a supersision of 0.72 g of addismritydride (as a 55% ww dispersion in mineral oil) in 30 mt of dehydrated dimethyformarride, and the resulting mixture was stirred at room temperature for 10 minutes, after which a solution of 3.57 g of d-t-buyl dicarbonate in 20 mt of dehydrated dimethyflormarride was added at room temperature and then mixture was stirred for 1 hour. At the end of this time, the reaction mixture was pound into ineventer and the resulting mixture was extracted with ethyl accetate. The extract was washed with water and hen with a saturated aquest of the solution of the solutio

PREPARATION 23

N-t-Butoxycarbonyl-N-methyl-4-methoxy-2-nitroaniline

A procedure similar to that described in Preparation 7 was repeated, except that 0.46 g of sodium hydride (as a 85% wire dispersion in mineral oil), 15 m of dehydrated dimethylformamide, 0.66 m lof methyl fodde and a solution of 1.9 g of N-1-butoxycarbonyl-4-methoxy-2-introaniline (prepared as described in Preparation 22) in 15 m lof dehydrated dimethylformamide were used, to give 2.0 g of the title compound having an RV value = 0.34 (on thin layer chromatography on siting agic diversioping solvent at 1.5 by volume mixture of diffy acadeta and hexans.

PREPARATION 24

55 N-Methyl-4-methoxy-2-nitroaniline

A procedure similar to that described in Preparation 8 was repeated, except that 2.0 g of N-t-butoxycarbonyl-N-methyl-4-methoxy-2-nitroaniline (prepared as described in Preparation 23) and 30 ml of a 4 N solution of hydrogen

chloride in 1,4-dioxane were used, to give 1.17 g of the title compound having an Rt value = 0.62 (on thin layer chromatography on silica gel; developing solvent: a 1:5 by volume mixture of ethyl acetate and hexane).

PREPARATION 25

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4-Methoxy-N-methyl-1.2-phenylenediamine

A solution of 1.16 g of N_methy4-methony2-introanline (prepared as described in Preparation 24) in 50 ml of othanol was shaken in an atmosphere of hydrogen and in the presence of 0.3 g of 10% why palladium-on-charcoal for 3 hours. At the end of this time, the palladium-on-charcoal was filtered off, and the filtrate was freed from the solvent by evaporation under reduced pressure, to give 1.17 g of the title compound having an F1 value = 0.50 (on thin layer chromatography on silice get, developing solvent x 1.3 by volume notiture of ethyl acetate and hoxano.

PREPARATION 26

Methyl 5-benzimidazolecarboxylate

A mixture of 10 g of 5-benzimidazoleoarboxylic acid, 150 ml of methanol and 100 ml of a 4 N solution of hydrogen chloride in 1-4 dictacen was aginted utharsonically for 4 hours. At the end of this time, the solvent was removed by distillation under reduced pressure, after which 300 ml of methanol and 3.5 g of lifetime borohydride were added to the residue and the mixture was stirred for 1 hour. The solvent was then removed by evaporation under reduced pressure and the residue was mixtured with an agreeous solution of soldium chloride, after which it was extracted with eithyl acetate. The solvent was removed by distillation under reduced pressure, to give 5.44 g of the title compound, metting at 136-138°C.

PREPARATION 27

Methyl 1-benzyl-5-benzimidazolecarboxylate

A mixture of 2.8 g of methyl 5-benzimidazolecarboxylate (prepared as described in Preparation 28), 3.52 g of baryl bornide, 3 g of potassilum carbonale and 50 ml of acetone was stirred for 3 days at room temperature. At the end of this time, the solvient was removed by everyation under reduced pressure and the residue was mixed with a squeucus solution of sodium chloride, after which it was extracted with ethyl acetate. The extract was dried over anily-drous sodium sulphate, after which the solvent was removed by distillation under reduced pressure. The residue was then recrystallized from a mixture of ethyl acetate and hexane, to give 0.94 g of the title compound, melting at 158-152°C.

PREPARATION 28

40 1-Benzyl-5-benzimidazolemethanol

0.87 g of methyl 1-benzyl-5-benzimickzolecarboxylate (prepared as described in Preparation 27) in 18 ml of depirated tetralydrotura were added to a suspension of 0.23 g of littime aluminum hydride in 10 ml of dehydrated tetralydroturam. Whilst ice-cooling, and the resulting mixture was stirred for 2 hours at room temperature. A further oil 1 g of littimum aluminum hydrids and 10 ml of dehydrated tetralydroturam were then added to the reaction mixture and the mixture was stirred for 1 hour at room temperature and then for 4.5 hours at 50 °C in oil bath, after which it was heated under refluxf or 2 hours. The reaction mixture was cooled to room temperature by allowing it to stand, after which sodium sulphate decarbydrate was added to it in excess and the mixture was stirred for 2 hours at room temperature. At the end of this time, the reaction mixture was filtered with the aid of a Celler fixed many's filter aid and the filtrate was freed from the solvent by distillation under reduced pressure. The residue was then creystallized from a mixture of ethanical and dissipancy of there, to give 38 mg of the title compound, molting at 148 - 150°C.

PREPARATION 29

55 5-[4-(1-Benzylbenzimidazol-5-ylmethoxy)benzyll-3-triphenylmethylthiazolidine-2.4-dione

A mixture of 822 mg of 5-(4-hydroxy/benzyl)-3-triphenylmethylthiazolidine-2,4-dione, 454 mg of azodicarbonyldipiperidine, 6 ml of dehydrated toluene and 0,44 ml of tributylohosohine was stirred for 30 minutes at room temperature.

All the end of this time, 349 mg of 1-benzyl-5-benzindszelemethanol were added to the reaction mixture and then the mixture was stirred for 3 hours, after which I was allowed to stand for 10 days at room temperature. The solvent was then removed by distillation under reduced pressure and the resulting residue was purified by column chromatography through allica get using a gradient eletion method, with mixtures of ethyl accetate each bexane in ratios ranging from 3: 10 to 1:0 by volume as the eleuter, by gwte 0.32 g of the tible compound, soldering at 90 - 91 the 30 of the state of the soldering at 90 - 91 the soldering at 91 the soldering at 90 - 91 the soldering at 90 - 91 the soldering at 90 - 91 the soldering at 91 the soldering at 90 - 91 the soldering at 91 the

FORMULATION 1

Powder preparation

4 g of 5 [4-(6-methoxy-t-methylbenzimidazol-2-yl-methoxy)benzyfithiazolidine-2,4-dione (Compound No. 1-49), 10 g of polyvinylgyrrolidone and 0.5 g of hydroxypropylmethyloellulose (Commercial name: TC-5E; a product of Shin-Elsu Chemical Industy Co., Ltd.), are mixed and pulverized using a vibratling mill for 30 minutes to obtain the desired powder preparation.

FORMULATION 2

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Capsule preparation

20 g of 6-[4-(6-methoxy-1-methylbenzimidazof-2-yl-methoxy)benzyl[jhiazolidine-2,4-dione (Compound No. 1-49) and 20 g of polyvinybyrrolidone are dissolved in a mixture of 100 g of destone and 100 g of othanol, and then the solution is sprayed onto 200 g of cross-carmellose sodium, using a fluidized bed granulator, to obtain granules. 0.1 g of trydroxypropy/methylcellulose (Commercial name; TO-6E; a product of Shin-Elsu Chemical Industry Co., Ltd.) and 1 g of lactose are then added to 10 g of these granules and mixed. A gelatin capsule is then filled with 0.24 g of this mixture, to obtain a capsule preparation. The capsule preparation contains 0.1 g of the active compound per capsule.

FORMULATION 3

Tablet preparation

1 g of 5-(4-(6-melloxy-1-melhyleanzimidazol-2-y-f-melhoxy)benzyllihiazoldine-2-4-dione (Compound No. 1-49) and 1 g of polyvinylpymolidone are dissolved in a mbture of 5 g of acetone and 5 g of ethenol, and then using a creary evaporator, the organic solvent is removed by evaporation under reduced pressure. The resulting solid matter is pulverized, to obtain fine granules. 0.25 g of orystatine cellulose, 0.05 g of hydroxyproyinethylicallusos (Commercial name: To-6E; a product of 5thin-Ethe Ohemical Industry Co., Ltd.), 0.18 g of laddose and 0.2 g of magnesium stearate are added to 1 g of these fine granules and mixed. Tablets are then prepared using a tableting machine.

40 Claims

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1. Compounds of formula (I):

$$X-(CH_2)_m-Y Z$$
(I)

in which:

X represents a benzimidazole group which is unsubstituted or is substituted by at least one of substituents α , defined below:

Y represents an oxygen atom or a sulphur atom:

Z represents a group of formula (i), (ii), (iii), (iv) or (v):

R represents:

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a hydrogen atom;

an alkyl group having from 1 to 4 carbon atoms;

(iv)

an alkoxy group having from 1 to 4 carbon atoms;

a halogen atom;

a hydroxy group;

a nitro group; a group of formula -NRaRb.

in which RP and RP are the same or different and each represents a hydrogen atom, an ality group having from 1 to 8 carbon atoms, an arrankyl group in which an allyl group having from 1 to 5 carbon atoms is substituted by a carbocyclic anyl group having from 6 to 10 carbon atoms; a carbocyclic anyl group having from 6 to 10 carbon atoms; an ailphatic acyl group having from 6 to 10 carbon atoms; an ailphatic acyl group having from 6 to 10 carbon atoms; an ailphatic acyl group having from 2 to 6 carbon atoms is substituted by at least one carbocyclic anyl group having from 6 to 10 carbon atoms; or an aromatic acyl group having from 7 to 11 carbon atoms: or

(v)

an aralkyl group in which an alkyl group having from 1 to 5 carbon atoms is substituted by a carbocyclic aryl group having from 6 to 10 carbon atoms; and

m represents an integer from 1 to 5;

said substituents a are selected from:

an alkyl group having from 1 to 4 carbon atoms:

an alkoxy group having from 1 to 4 carbon atoms; a benzyloxy group;

a halogen atom;

a hydroxy group;

an acetoxy group;

a phenyithio group:

an alkylthic group having from 1 to 4 carbon atoms:

- a trifluoromethyl group:
- a nitro group;

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- a group of formula -NRaRb, in which Ra and Rb are as defined above;
 - a a carbocyclic aryl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by at least one of substituents β, defined below,

an aralkyt group in which an alkyt group having from 1 to 5 carbon atoms is substituted by a carbocyclic anyl group which has from 6 to 10 carbon atoms and which is unsubstituted or is substituted by at least one of substitutes 8, defined below;

said substituents β are selected from allyling incups having from 1 to 4 carbon atoms, alloxy groups having from 1 to 4 carbon atoms, halogon atoms, halogon atoms, halogon atoms, halogon atoms, halogon atoms, because of the must be a carbon atoms, halogon atoms of the must be a carbon atoms of the must

 A compound according to Claim 1, in which X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents a', defined below.

substituent of represents an alkyl group having from 1 to 4 carbon atoms, an altroxy group having from 1 to 4 carbon atoms, a benzylory group, a halogen atom, a hydroxy group, an acetoxy group, a phenythilo group, an alkythio group having from 1 to 4 carbon atoms, a trifluoromethyl group, a nitro group, an amino group of formula -NFPePs.

in which P^b and P^b are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 8 carbon atoms, an araklyl group having from 7 to 11 carbon atoms, an anyl group having from 6 to 10 carbon atoms, an ailphatic acyl group having from 1 to 11 carbon atoms, an anyl-allphatic acyl group having from 8 to 12 carbon atoms or an aromatic acyl group having from 7 to 11 carbon atoms.

an aryl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by at least one of substituents 8.

said substituent β represents an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a halogen atom, a hydroxy group, a nitro group, a phenyl group, a trifluoromethyl group or an amino group of formula -NPRPh, in which PR and PR are as defined above;

or an aralkyl group having from 7 to 11 carbon atoms which is unsubstituted or is substituted by at least one of substituents β.

- A compound according to Claim 1 or Claim 2, in which R represents a hydrogen atom, an alkyl group having from
 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms or a halogen atom.
 - 4. A compound according to Claim 1, in which:

X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents α' , defined below.

substituent of represents an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a benzyboxy group, a halogen atom, a hydroxy group, an acetoxy group, aphenythio group, an alkylthio group having from 1 to 4 carbon atoms, a trifluoromethyl group, a nitro group, an amino group of formula - NPPPP.

in which R⁴ and R⁵ are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 8 carbon atoms, an arallyl group having from 7 to 11 carbon atoms, an aryl group having from 6 to 10 carbon atoms, an aliphatic acyl group having from 1 to 11 carbon atoms, an anyl-aliphatic acyl group having from 7 to 11 carbon atoms, an aryl-aliphatic acyl group having from 7 to 11 carbon atoms.

an anyl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by at least one of substitutents 6.

said substituent \$\beta\$ represents an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having

from 1 to 4 carbon atoms, a halogen atom, a hydroxy group, a nitro group, a phenyl group, a trifluoromethyl group or an amino group of formula -NR^aR^b, in which R^a and R^b are as defined above;

or an aralkyl group having from 7 to 11 carbon atoms which is unsubstituted or is substituted by at least one of substituents β: and

R represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms or a halogen atom.

- A compound according to any one of Claims 1 to 4, in which Y represents an oxygen atom.
 - A compound according to any one of Claims 1 to 5, in which Z represents a 2,4-dioxothiazolidin-5-ylidenylmethyl, 2,4-dioxothiazolidin-5-ylmethyl or 2,4,-dioxooxazolidin-5-ylmethyl group.
- 7. A compound according to Claim 1, in which:

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X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents α' , defined below:

- substituent of represents an alkyl group having from 1 to 4 cathon atoms, an alloxy group having from 1 to 4 cathon atoms, a benzyloxy group, a halogen atom, a hydroxy group, an aclosty group, a phenythiol group, an alkythio group having from 1 to 4 cathon atoms, a trifluoromethyl group, a nitro group, an armino group of formula JNRPP.
- in which R^a and R^b are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 8 carbon atoms, an aralkyl group having from 7 to 11 carbon atoms.
- an anyl group having from 6 to 10 carbon atoms, an aliphatic acyl group having from 1 to 11 carbon atoms, an anyl-aliphatic acyl group having from 8 to 12 carbon atoms or an aromatic acyl group having from 7 to 11 carbon atoms, an anyl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by at least one of substituents §,
- substituent β represents an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a halogen atom, a hydroxy group, a nitro group, a phenyl group, a trifluoromethyl group or an amino group of formula -NPAPP, in which PP and PP are as defined above,
- 35 or an aralkyl group having from 7 to 11 carbon atoms which is unsubstituted or is substituted by at least one of substituents β;

Y represents an oxygen atom;

- Z represents a 2,4-dioxothiazolidin-5-ylidenylmethyl, 2,4-dioxothiazolidin-5-ylmethyl or 2,4,-dioxooxazolidin-5-ylmethyl group: and
 - R represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms or a halogen atom.
- A compound according to any one of Claims 1 to 7, in which X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents of, defined below;
 - substituent of operants an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a benzyloxy group, a hatopen atom, a hydroxy group, an aceloxy group, a preyntylloxy an alkylthio group having from 1 to 4 carbon atoms, a trifluoromethyl group, a nitro group, an amino group of formula -NPEPP.
 - in which FN and FN are the same or different and each represents a hydrogen atom, an allylig roup having from 1 to 8 carbon atoms, an analylig group having from 7 to 11 carbon atoms, an aright group having from 6 to 10 carbon atoms, an aliphatic acyl group having from 1 to 11 carbon atoms, an aryl-alphatic acyl group having from 8 to 12 carbon atoms or an aromatic acyl uroup having from 7 to 101 carbon atoms, and

an anyl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by from 1 to 3 substit-

uents selected from substituents 6.

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substituent β represents an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 carbon atoms, a halogen atom, a hydroxy group, a niting group, a phenyl group, a trifluoromethyl group or a raming group of formula -NPEP\$, in which Pa and Pa are as defined above,

or an arallyl group having from 7 to 11 carbon atoms which is unsubstituted or is substituted by from 1 to 3 substituents selected from substituents 8.

- A compound according to any one of Claims 1 to 8, in which Z represents a 2,4-dioxothiazolidin-5-yildenylmethyl or 2.4-dioxothiazolidin-5-yilmethyl group.
- A compound according to any one of Claims 1 to 9, in which R represents a hydrogen atom, a methyl group, a methoxy group, an ethoxy group, a fluorine atom or a chlorine atom.
- 15 11. A compound according to any one of Claims 1 to 10, in which m represents an integer from 1 to 3.
 - 12. A compound according to Claim 1, in which:

X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents α', defined below;

substituent of represents an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a benzyloxy group, a halogen atom, a hydroxy group, an acetoxy group, aphenythio group, an alkylthio group having from 1 to 4 carbon atoms, a trifluoromethyl group, an anitro group, an amino group of formula - NPPPP.

in which F^a and F^b are the same or different and each represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, an arailyl group having from 7 to 11 carbon atoms, an aryl group having from 6 to 10 carbon atoms, an aliphatic acyl group having from 1 to 11 carbon atoms, an aryl-alphatic acyl group having from 8 to 12 carbon atoms or an aromatic acyl group having from 7 to 11 carbon atoms.

an anyl group having from 6 to 10 carbon atoms which is unsubstituted or is substituted by from 1 to 3 substituents selected from substituents β_1

substituent β represents an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a halogen atom, a hydroxy group, a nitrogroup, a phenyl group, a trifluoromethyl group or an amin

or an aralkyl group having from 7 to 11 carbon atoms which is unsubstituted or is substituted by from 1 to 3 substituents selected from substituents 8:

40 Y represents an oxygen atom;

Z represents a 2,4-dioxothiazolidin-5-ylidenylmethyl or 2,4-dioxothiazolidin-5-ylmethyl group;

R represents a hydrogen atom, a methyl group, a methoxy group, an ethoxy group, a fluorine atom or a chlorine atom: and

m represents an integer from 1 to 3.

 A compound according to any one of Claims 1 to 12, in which X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents q", defined below.

substituent of represents an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a benzyloxy group, a halogen atom, a phenylthio group, an alkylthio group having from 1 to 4 carbon atoms, a tiffucomently group, a hydroxy group, an acetoxy group, a benzyl group or a phenyl group.

- 55 14. A compound according to any one of Claims 1 to 13, in which Z represents a 2,4-dioxothiazolidin-5-ylmethyl group.
 - A compound according to any one of Claims 1 to 14, in which R represents a hydrogen atom, a methyl group or a methoxy group.

16. A compound according to Claim 1, in which:

X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents α^* , defined below:

substituent of 'represents an alkyl group having from 1 to 4 carbon atoms, an alkoxy group having from 1 to 4 carbon atoms, a benzyloxy group, a halogen atom, a phenylthic group, an alkylthic group having from 1 to 4 carbon atoms, a trifluoromethyl group, a hydroxy group, an acetoxy group, a benzyl group or a phenyl group;

10 Y represents an oxygen atom;

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- Z represents a 2,4-dioxothiazolidin-5-ylmethyl group;
- R represents a hydrogen atom, a methyl group or a methoxy group; and
- m represents an integer from 1 to 3.
- 17. A compound according to any one of Claims 1 to 16, in which X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents o.", defined below;

substituent α" represents a methyl group, an ethyl group, an isopropyl group, a methoxy group, an ethoxy group, a propoxy group, an espondown group, an espondown an ethyling group, an espondown group group group, an espondown group g

- 18. A compound according to any one of Claims 1 to 17, in which R represents a hydrogen atom.
- 19. A compound according to any one of Claims 1 to 18, in which m represents the integer 1 or 2.
- 20. A compound according to Claim 1, in which:
- 30 X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents α", defined below:

substituent a" represents a methyl group, an ethyl group, an isopropyl group, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a benzyloxy group, a fluorine atom, a chlorine atom, a phenylithio group, a methylthio group, an ethylthio group, a hydroxy group, an acetoxy group, a benzyl group or a phenyl forum:

- Y represents an oxygen atom;
- Z represents a 2,4-dioxothiazolidin-5-ylmethyl group;
- R represents a hydrogen atom; and
 - m represents the integer 1 or 2.
- 45 21. A compound according to any one of Claims 1 to 20, in which X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents α**, defined below;

substituent α^{**} represents a methyl group, a methoxy group, a hydroxy group, a benzyl group or an acetoxy group.

- 22. A compound according to any one of Claims 1 to 21, in which m represents the integer 1.
 - 23. A compound according to Claim 1, in which:

X represents a benzimidazole group, which is unsubstituted or is substituted by from 1 to 5 of substituents α'''', defined below:

substituent α^{eff} represents a methyl group, a methoxy group, a hydroxy group, a benzyl group or an acetoxy group.

- Y represents an oxygen atom:
- Z represents a 2,4-dioxothiazolidin-5-ylmethyl group;
- R represents a hydrogen atom; and

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- m represents the integer 1.
- 24. 5-[4-(1-Methylbenzimidazol-2-ylmethoxy)benzyl]-thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof
 - 5-[4-(6-Methoxy-1-methylbenzimidazol-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable saits thereof.
- 5-{4-(5-Methoxy-1-methylbenzimidazol-2-ylmethoxy)-benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.
 - 5-{4-(1-Benzylbenzimidazol-5-ylmethoxy)benzyl]-thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.
 - 5-{4-(5-Hydroxy-1,4,6,7-tetramethylbenzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.
 - 5-[4-(5-Acetoxy-1.4,6,7-tetramethylbenzimidazol-2-ylmethbxy)benzyl]thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof.
 - 30. A pharmaceutical composition for the treatment or prophylaxis of insulin resistance, diabetes, hyperglycemia, arteriosclerosis, cataracts, hyperfiperiia, obesity, impaired glucose tolerance, hyperfiencion, polycystic ovary syndrome, gestational diabetes mellitus or insulin resistant non-161, cataracts and complications thereof, which composition comprises an effective amount of an active compound in admixture with a pharmaceutically acceptable carrier or diffuent, in which said active compound is at least one orepound according to any one of Claims 1 to 28.
 - 31. The use of a compound according to any one of Claims 1 to 29 for the manufacture of a medicament for the treatment or prophylaxis of insulin resistance, diabetes, hyperglycemia, arterioscierosis, hyperilosemia, obesity, impaired glucose tolerance, hypertension, polycystic ovary syndrome, gestational diabetes mellitus or insulin resistant non-IGT, cataracts and complications thereof.
 - 32. A pharmaceutical composition for the inhibition of aldose reductase, 5-lipoxygenase or lipid peroxide, and complications thereof, which composition comprises an effective amount of an active compound in admixture with a pharmaceutically acceptable carrier or diluent, in which said active compound is at least one compound according to any one of Claims 1 to 29.
 - 33. The use of a compound according to any one of Claims 1 to 29 for the manufacture of a medicament for the inhibition of aldose reductase, 5-lipoxygenase or lipid peroxide, and complications thereof.
 - 34. The use of a compound according to any one of Claims 1 to 29 for the manufacture of a medicament.



EUROPEAN SEARCH REPORT

Application Number EP 96 30 3940

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